A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS- TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT

DISSERTATION SUBMITTED FOR

M.D GENERAL MEDICINE

BRANCH – I

APRIL 2015

THE TAMILNADU DR.M.G.R.

MEDICAL UNIVERSITY CHENNAI,

TAMILNADU,INDIA

CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled "A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS-TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT " is the bonafide work of Dr. ARUN KUMAR.A., in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2015.

Capt.Dr.B.SANTHAKUMAR
M.Sc (F.Sc)., M.D (F.M), PGDMLE,
Dip. N.B (F.M)
Dean, Madurai Medical College

CERTIFICATE FROM THE HOD

This is to certify that the dissertation entitled "A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS-TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT" is the bonafide work of Dr. ARUN KUMAR.A., in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2015.

Dr. S.Vadivel Murugan, M.D
Professor and HOD,
Department of General Medicine,
Madurai Medical College,
Madurai.

CERTIFICATE FROM THE GUIDE

This is to certify that the dissertation entitled "A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS-TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT" is the bonafide work of Dr. ARUN KUMAR.A., in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2015.

Dr.M.Natarajan, M.D.
Professor,
Department of General Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

DECLARATION

I, Dr.ARUN KUMAR.A., solemnly declare that, this dissertation "A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS-TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT" is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of Dr.M.NATARAJAN, M.D, Professor, Department of General Medicine, Madurai Medical College, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch-I;** examination to be held in **April 2015.**

Place: Madurai

Date:

Dr.ARUNKUMAR.A

ACKNOWLEDGEMENT

I would like to thank **Capt. Dr.B. SANTHAKUMAR M.Sc (F.Sc)., M.D (F.M), PGDMLE, Dip. N.B (F.M)** Dean, Madurai Medical College, for permitting me to utilize the facilities of Madurai Medical College and Government Rajaji Hospital facilities for this dissertation.

I wish to express my respect and sincere gratitude to my beloved teacher and Head of the Department, **Prof.Dr.S.VADIVELMURUGAN, M.D.,** Professor of Medicine for his valuable guidance and encouragement during the study and also throughout my course period.

I would like to express my deep sense of gratitude, respect and thanks to my beloved Unit Chief and Professor of Medicine, **Prof.Dr.M.NATARAJAN, M.D.,** for his valuable suggestions, guidance and support throughout the study and also throughout my course period.

I am greatly indebted to my beloved Professors, **Dr.V.T.PREMKUMAR, M.D., Dr.R.BALAJINATHAN, M.D., Dr.G.BAGHYALAKSHMI, M.D., Dr.J.SANGUMANI, M.D., Dr.C.DHARMARAJ, M.D.,** and **Dr.R.PRABHAKARAN, M.D.,** for their valuable suggestions throughout the course of study.

I express my special thanks to **Dr.C.RAMESH, M.D., D.T.C.D.,** Retired Professor of Thoracic Medicine for permitting me to utilize the

facilities in the Department for the purpose of this study and guiding me with enthusiasm throughout the study period.

I express my special thanks to **Dr.MOSES.K.DANIEL, M.D.,** Retired Professor of Medicine for his guidance and support during the study.

I am extremely thankful to Assistant Professors of Medicine of my Unit, **Dr.K.MURALIDHARAN, M.D., Dr.B.PALANIKUMAR, M.D., Dr.P.K.GANESH BABU., M.D.,** and **Dr.G.SELVARANI, M.D.,** for their valid comments and suggestions.

I sincerely thank the Assistant Professors of Thoracic Medicine, **Dr.K.BHARATHI BABU, M.D. (Chest)** and **Dr.R.PRABHAKARAN, M.D. (Chest)** for their guidance and suggestions in my dissertation work.

I express my special thanks to the Assistant Professor of Medicine **Dr.S.C.VIVEKANANDHAN, M.D., D.T.C.D.,** for his suggestions and guidance.

I sincerely thank all the staffs of Department of Medicine and Department of Thoracic Medicine for their timely help rendered to me, whenever and wherever needed.

I extend my thanks to all my friends, batch mates and my junior and senior colleagues who have stood by me and supported me throughout my study and course period.

Finally, I thank all the patients, who form the most vital part of my work, for their extreme patience and co-operation without whom this project would have been a distant dream and I pray God, for their speedy recovery.

CONTENTS

ABSTRACT

A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS- TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT

Background:

A variety of pulmonary manifestations are associated with Rheumatoid arthritis; lung disease is the second most common cause of death (18%) after infection (27%) in patients with RA. Pulmonary function test abnormalities in RA can be restrictive (19-44%) if there is pleural or parenchymal involvement, or obstructive (16-38%) if there is obliterative bronchiolitis, bronchiectasis or cricoaryetenoid arthritis. The incidence of pulmonary function test abnormalities in various studies done in patients with RA varies widely.

Objective:

1. To assess the proportion of pulmonary function test (PFT) abnormalities in patients with rheumatoid arthritis.
2. To categorize the PFT abnormalities as obstructive or restrictive and further quantify them as mild, moderate or severe.
3. To compare PFT abnormalities between treatment naïve and on treatment group.

Methods:

A pretested semi structured questionnaire was administered to newly diagnosed and those patients on treatment for rheumatoid arthritis. They underwent routine historical evaluation, physical examination and detailed respiratory and musculoskeletal examination. Then they underwent pulmonary function testing, chest radiography and pulse oximetry. The parameters recorded in spirometry were FEV_1, FVC, PEF and FEF25-75%. The spirometer was selected and calibrated in accordance with ATS guidelines. The criteria for obstruction and restriction were selected in accordance with ATS guidelines

Results:

In our study fifty patients were included, 25 newly diagnosed and 25 patients on treatment for minimum 3 years. The male to female ratio in this study was 1:2. The mean age of patients was 46.5±10.5 years. Rheumatoid factor was positive in 35 (70%) patients. 16% of patients had respiratory symptoms. Incidence of radiological abnormality was 10.7%.

Fifty patients underwent pulmonary function testing. 56% patients had abnormal PFTs 16% had obstructive and 40% had restrictive pattern in treatment naive and 64% patient had abnormal PFTs 20% had obstructive and 44% had restrictive pattern in on treatment group.

The incidence of PFT abnormality in the age group of 50-59 was highest. This was not statistically significant. The number of patients with restrictive PFTs increased after three years of disease duration when compared with newly diagnosed patients. The number of patients with obstructive PFTs also increased when the disease duration was more than 3 years. No statistical correlation was found between the severity of PFT abnormality (both obstruction and restriction) and the disease duration. The number of abnormal PFTs increased as the functional class of RA increased.

Interpretation and conclusion:

The number of abnormal PFTs increased as the disease duration increased. There was no correlation between the disease duration and the severity of PFT abnormality. PFT abnormalities were encountered with greater frequency in patients of higher functional class of disability in rheumatoid arthritis. There is increased incidence of PFT abnormality in on treatment group when compared to treatment naive group this may be explained by the type of lung involvement (ex. If the patient had usual interstitial pneumonia the lung disease may progress or remain static) but a longitudinal study is warranted. Pulmonary function testing when combined with chest radiography is cost effective and a good screening test for early detection of pleuro pulmonary involvement in patients with RA.

KEYWORDS:

PFT, Obstruction, Restriction, Functional class.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multi-system disease of unknown cause. It is a systemic inflammatory disease and affects 1-2% of the general population. The characteristic feature of RA is inflammatory synovitis that is persistent and involves most of the peripheral joints depending on the duration of disease causing cartilaginous and bony erosions. In general population, RA is found in 0.8% of people and its prevalence increases with advancing age [1]. The onset of RA is more common in the age group of 40- 50 years

The mortality and morbidity of RA is mostly attributed to its extraarticular involvement. Extra-articular manifestations are seen in nearly 50% of patients with RA, the commonly affected sites being the skin, eye, heart, and lungs[4]. In 40% of patients the prevalence of extraarticular manifestation are so severe clinically.

A wide range of pulmonary manifestations are seen in patients with RA. The involvement of lung is the second most common cause of death (18%) after infection (27%) in patients with RA[6]. In men pleuro-pulmonary manifestations are more common compared to women[7]. Among pulmonary manifestation Rheumatoid pleurisy is the most

common intrathoracic manifestation of rheumatoid arthritis [8].Pleural effusion is clinically evident in only 5% of patients with rheumatoid pleurisy[9].

Similarly, the incidence of pleural effusion depends on the duration of disease. Pleural effusions seen most frequently with longstanding active articular disease. These patients also have rheumatoid nodules [10,11]. Prospective studies using high resolution computed tomography [HRCT] of the lungs demonstrated that in 20% of patients, there is associated fibrosing alveolitis [12].Both ILD and pleural effusion can precede articular symptoms.

Parenchymal involvement in RA may be in the form of rheumatoid nodules, Caplan syndrome and interstitial lung disease. The only specific pulmonary lesion in these patients were rheumatoid nodules. They are single or multiple nodules seen more commonly in males. Similarly nodules are common among those with subcutaneous nodules and extra-articular manifestations. Caplan's syndrome is one such seen in silica exposed patients with bilateral pulmonary nodules who have rheumatoid arthritis.

The incidence of interstitial lung disease [ILD] in RA has been found to be19- 44%in a study conducted by Dawson et al It is more common in men who are seropositive and aged between 50-60 years of age[16].

RA can affect airways of all diameter and can cause varying disease manifestation[17-19]. Upper airway involvement includes cricoarytenoid arthritis, rheumatoid nodules in the vocal cords and vocal cord paresis. Lower airway involvement includes bronchiectasis, bronchiolitis with or without organizing pneumonia. There is a high incidence of radiographic bronchiectasis, up to 30% in some HRCT studies [20-22].Pulmonary involvement can be studied using HRCT and DLCO for anatomical and physiological abnormalities respectively .However these diagnostic tests may not be widely available and cost effective. Pulmonary function testing using an office spirometer is a simpler, cheaper and more widely available tool for screening patients with RA for pulmonary involvement.

Pulmonary function test abnormalities in RA can be restrictive (19-44%) if there Is pleural or parenchymal involvement, or obstructive (16-38%) if there is obliterative bronchiolitis, bronchiectasis or cricoaryetenoid arthritis[23].

The incidence of pulmonary function test abnormalities in various studies done in patients with RA varies widely.

Although the patients with RA have varying degree of severity in the manifestation of pulmonary function, the progression of the disease severity may or may not be altered by the immunosuppressive therapy. The prognosis in these patients are guarded.The purpose of this study is to assess the incidence and type of PFT abnormality in patients with rheumatoid arthritis presenting to a tertiary care hospital and also to compare PFT abnormalities between treatment naïve and on treatment group.

AIMS AND OBJECTIVES

- To assess the proportion of pulmonary function test (PFT) abnormalities in patients with rheumatoid arthritis.
- To categorize the PFT abnormalities as obstructive or restrictive and further quantify them as mild, moderate or severe.
- To compare the PFT abnormality in treatment naïve and patients on treatment for rheumatoid arthritis.

REVIEW OF LITERATURE

Rheumatoid arthritis (RA) is one of the functionally disabling disease that is common among general population and various genetic and environmental contributes to its development. It occurs in approximately 1% of the population. The disease is characterized by inflammation of synovial membranes and articular structures, which are the primary target of the inflammatory process. Inflammation and degeneration along with proliferation of synovial membrane typify the disease. Joint deformities and disability result from the e rosion and destruction of synovial membranes and articular surfaces [24].

RA usually affects the joints in a symmetric manner. The disease is polyarticular and involves most of the small joints with exception to the distal interphalangeal (DIP) joints [25]. The joints most commonly affected are Wrists, proximal interphalangeal, metacarpophalangeal, followed by metatarsophalangeal and shoulders.

The least commonly affected are the hips and spine. Temporomandibular and cervical spine involvement can occur in early stage of the disease in certain patients [26]. In patients who have unilateral

involvement, the other joints on the same side of the body may be affected. The arthritis in RA predominantly involves peripheral joints. Early wrist and metatarsophalangeal joint involvement is an indicator of progression to severe RA[26]

There is also involvement of extra-articular structures in RA. The predominant one among this is subcutaneous nodules and pleuro-pulmonary manifestations. Other organs to be affected are cardiovascular and nervous system. Vasculitis and Felty's syndrome are rare manifestations but may be severe enough to cause disability[27]. The occurrence and course of the extraarticular manifestations of RA does not always parallel joint disease[28]. Extraarticular manifestations of RA are described in Table1.

Most common cause of death in patients with RA includes mostly cardiac followed by pulmonary complication. Mortality due to pulmonary complications is about 10 to 20% in patients with RA [28,30,31]. Although pulmonary infection and/ or drug toxicity are frequent complications, lung disease directly related to underlying RA is more common. The mortality ratio of patients with RA is about 2.5 to 5% when compared with control[28,30].

The majority of lung disease occurs within the first 5years after the initial diagnosis. In 10 to 20 % of patients it may be the initial manifestation of the disease. The lung parenchyma, any type of airways,

pulmonary vasculature and pleura can all be involved, with variable clinical features. [Table2]

Table1.Extra-articular manifestations of RA

SITE	MANIFESTATIONS
Systemic	Fever, Weight Loss, Fatigue, Susceptibility to infection
Musculoskeletal	Musclewasting, Bursitis, Tenosynovitis, Osteoporosis
Hematological	Anemia, Thrombocytosis, Eosinophilia
Lymphoreticular	Splenomegaly, Felty Syndrome
Cutaneous	Nodules, Ulcers, Sinuses, Fistulae
Ocular	Episcleritis, Scleritis, Scleromalacia, Keratoconjunctivitis Sicca
Vasculitis	Digital Arteritis, pyoderma Gangrenosum, Mononeuritis Multiplex
Cardiac	Pericarditis, Myocarditis, Endocarditis, Conduction Defects, Coronary
Neurological	Cervical Cord Compression, Compressive Neuropathies, Peripheral
Pulmonary	Nodules, Pleuraleffusions, Fibrosingalveolitis, Bronchiolitis, Caplan Syndrome
Others	Amyloidosis

Table2.Pleuropulmonary manifestations of rheumatoid arthritis

SITE	MANIFESTATIONS
PLEURA	Pleuritis, Pleural effusion, Empyema Pneumothorax
INTERSTITIUM	Organizing Pneumonia, Usual interstitial Pneumonia
AIRWAYS	Constrictive Bronchiolitis (bronchiolitis Obliterans)
ti VASCULAR	Pulmonary Hypertension, Pulmonary Vasculitis
OTHER	Cricoarytenoid Arthritis, Bullous Lung Disease

PLEURAL INVOLVEMENT

Pleuritis and pleural effusions:

Pleuritic type of chest pain occurs in 25% of patients with RA [32].Five percent of patients with RA develop pleural effusions which are small to moderate, unilateral being more common than bilateral [33].Pleural disease is more common in middle aged men. Pleural effusions are more common in patients with longstanding active articular disease and rheumatoid nodules[34,35]. Rarely , pleural effusion may precede joint disease [36].Small effusions usually resolve spontaneously within weeks; however, they may persist and present as chronic pleural effusion .Large effusions need therapeutic aspiration and tend to recur after aspiration.

The triad of multinucleated macrophages, large elongated macrophages, and under a background of granular debris is characteristic of the pleural fluid cytology in rheumatoid effusions [37-39]. Pseudochylous effusions can also occur with RA[35,40]. Rheumatoid effusions are usually exudative with very low glucose levels and are lymphocyte predominant[41].

In upto 20% of patients with rheumatoid arthritis and associated pleural effusion, prospective studies show fibrosing alveolitis on HRCT. Rarely, pneumothorax or pyothorax can occur from ruptured necrotic rheumatoid nodule[45].

The most common pulmonary function abnormality in rheumatoid pleural effusion is restriction which worsens when the patient develops fibrothorax[46]. The restriction is associated with paradoxically increased DLCO which distinguishes it from interstitial lung disease where the DLCO is reduced.

PARENCHYMAL INVOLVEMENT

Pulmonary parenchymal involvement can develop in RA during the course of the disease or it may be the initial manifestation occurring in very early stages of disease.

Rheumatoid nodules:

The only specific pulmonary lesions observed in patients with RA is pulmonary nodules. Rheumatoid (necrobiotic) nodules are found

20% of patients[47,48]. They are either single or multiple in number usually measuring 1-3cm, although nodules measuring upto 10cm may be seen [49]. Rheumatoid nodules are seen more commonly in males. Nodules are commonly found sub-pleurally in the upper and Mid zones of the lung; rarely they can occur endobronchially. In some case multiple widespread nodules are described.

In Caplan syndrome, pneumoconiosis and RA are synergistic and produce as severe fibroblastic reaction with obliterative granulomatous fibrosis. Pathologically, the granulomas consist of collections of lymphocyte, macrophages, plasmacells and histiocytes under the background of necrotic debris. [52]. These nodules must be differentiated from malignant ones which is done by HRCT and biopsy. These nodules when subpleural can lead to empyema or pneumothorax on rupture. Other complication is presenting as hemoptysis. Spirometric evaluation in rheumatoid nodules is reveals restriction [54]. In some patients similar to ankylosing spondylitis apical fibrobullous disease and aspiration pneumonitis can occur.

Interstitial Lung Disease:

The incidence of ILD in RA has been found to be 19-44% in a study conducted by Dawson et al. It occurs more frequently in seropositive men aged between 50-60years[16]. High titres of RF and presence of rheumatoid nodules are associated with increased prevalence of pulmonary fibrosis in RA[55,56].

Active or previous tobacco smoking and rheumatoid factor (RF) seropositivity are risk factors for the development and severity of ILD in patients with RA[57-60]. A correlation has been proposed between the habit of cigarette smoking and the presence of HLA-DRB1" shared epitope"(SE), anticyclic citrullinated peptide antibody(anti- CCP), and the development of RA[61]. The presence of smoking with associated two copies of the HLA-DRSE genes increased the risk for RA 21-fold compared non smokers with absent gene.

In some patients smoking has been independentally associated with ILD. Patient with more than 25 pack years have 3.76 % incidence of 95% confidence limit. When with RA the incidence increases.

The increased reactivity of mesenchymal cells in RA is postulated as the cause of pulmonary fibrosis. In this disorder when there is acute insult to lung parenchyma, there is activation of fibroblast which causes chronic inflammatory change leading to the endpoint of pulmonary fibrosis and tissue destruction[66].

Modes of presentation of RA associated ILD:

1. ILD may be incidentally detected on chest radiograph or abnormal screening spirometry in an aymptomatic patient with RA.

2. Diagnosis may occur during screening for high-risk occupational exposure, such as asbestosis.

3. Clinically overt disease may present insidiously and progress slowly [chronic ILD]. It may also present acutely,sub-acutely or have a relapsing remitting course. Disorders with chronic, insidious,and slowly progressive courses are those that most resemble IPF and usually share a common pathology (ie,UIP). Pulmonary fibrosis in RA can occur as a side effect of certain disease modifying agents [eg.,methotrexate].

Cryptogenic organizing pneumonia[COP]:

Cryptogenic Organising pneumonia is seen more common in rheumatoid arthritis when compared to other connective tissue disorders[67].It usually involves terminal bronchioles and distal air spaces. It is characterized by presence of plugs of granulation tissue in the airspaces. The main pathophysiology of COP is lymphocytic infiltration within bronchiolar walls and surrounding interstitium it usually shows multifocal consolidation on computed tomography when compared to bronchiolitis obliterans PFT shows restrictive pattern.[68]. It responds better to corticosteroids. The clinical presentation of COP initially is similar to a flu like illness, which is gradually progressive in nature. It takes weeks or months to develop a full blown disease characterized by dyspnea or exercise intolerance. The disease course may vary from spontaneous remission to progressive disorder. Steroids are the mainstay of therapy and disease may reccur on withdrawal of drug. Some patients may progress to end-stage fibrotic lung disease.

Acute Interstitial pneumonia:

Occasionally ILD in RA can present acutely. The most common pattern with this presentation is AIP. It is an idiopathic form of lung disease which is more severe in presentation. It has a similar histopathology as that of adult respiratory distress syndrome (ARDS) with diffuse alveolar damage(DAD). These patients usually have no no antecedent history. These patients progress rapidly to respiratory failure. These patients does not respond to any treatment steroids or immunosuppressive therapy. Clinical finding is similar to idiopathic pulmonary fibrosis. They are usually cyanotic with fine end-inspiratory pulmonary rales (Velcro rales). .Digital clubbing may accompany many of these disorders. They may present with right heart failure in advanced cases. Of all the histological patterns of ILD, the non specific interstitial pattern is the most prevalent[69] although in one study, most common pattern is usual interstitial pneumonia.

Usually the prognosis of interstitial lung disease in RA is good. There is slow deterioration of lung function in RA associated ILD. “However, one study reported a median survival of 3.5years and a 5-year survival rate of 39% in 49 patients with RA hospitalized for interstitial

pulmonary fibrosis, survival very similar to what is observed in patients with idiopathic pulmonary fibrosis[71].The investigation of choice to detect interstitial pneumonia is HRCT. It is abnormal in upto 80% of patients The prevalence of radiological evidence of pulmonary fibrosis in patients who have rheumatoid arthritis ranges from 2-10%[72]. The most representative data has come from a study in which chest radiographs of 309 patients who have rheumatoid disease were compared with those of age and sex matched controls[73].In this study a reticulonodular pattern consistent with fibrosis was seen in 4.5% of patients with rheumatoid disease v/s 0.3% of controls.The pattern and distribution of fibrosis on both CXR and HRCT are indistinguishable from those of IPF. In early stage, the radiographic appearance consists of irregular linear opacities causing a fine reticular or reticulonodular pattern[74]. The abnormality usually involves the lower lung zones[75].

Pulmonary function tests(PFTs) with the diffusing capacity of the lung for carbon monoxide (DLCO) are sensitive tests to detect RA associated

ILD. Evidence of restriction on lung function testing is found in 30-40% of all patients with RA associated ILD[77].The important functional defect is impairment of alveolo-capillary gas exchange with reduced diffusion capacity best measured utilizing single breath carbon monoxide diffusion capacity. Even though the prevalence of a restrictive defect in consecutive patients was not high (5-15%)[78-81] reduced DLCO was observed in more than 50% of patients with rheumatoid arthritis [82,84] and reduced DLCO was suggested to be the most sensitive marker of interstitial pneumonia on high-resolution computed tomography (HRCT).

In a study conducted by Laitinen O et al, vital capacity (VC) and single-breath diffusing capacity for carbon monoxide of the lungs (DLCO) were measured and chest X-ray evaluated in 129 patients with rheumatoid arthritis (RA)[83].Findings in the123 cases were observed as follows : in one of the lung function tests or X-ray examinations , 35%; abnormal X-rays,18%; reduced VC or Dco , 28% ; simultaneously low VC and Dco, 7%; and pathological findings in all three tests, 2%.The patients with abnormal X-rays showed extremely low VC and Dco values .Changes in respiratory function involved restrictive impairment and diffusion defects, and the results further implied that restrictive changes develop early, whereas decreased diffusion capacity is associated with more advanced

rheumatoid lung .The disparity abnormal findings in chest radiographic changes and lung function tests suggests that, both radiographic methods and pulmonary function tests should be used for evaluating pulmonary manifestations in patients with RA.

In a study by Gabbay et al in 1997,abnormalities consistent with ILD were found in one or more investigation in 58% of patients with RA.(PFT in 22%,DTPA nuclear scaning 15%, HRCT in 33% and chest radiograph in 6%.Hence,PFT was a sensitive measure in picking up pulmonary abnormalities[85]

Fibrosing alveolitis is a common serious complication of RA. In a study conducted by Dawson et al,19% had fibrosing alveolitis ;most frequently reticular pattern on HRCT, 14% had restrictive PFT[16] A distinctive manifestation of rheumatoid lung disease is progressive upper lobe fibrosis and cavitation .Patients with this disease may be asymptomatic and present only as a radiological abnormality.

AIRWAY DISEASE IN RA:

RA can cause upper, lower, and small, distal airway disease [17-19].

Upper airway disease:

Cricoarytenoid arthritis is a frequent manifestation of RA that presents with symptoms of foreign body sensation in throat, soreness, and throat pain which radiates to the ears. Some patients may present with dysphonia, dysphagia and stridor. In a study conducted by Hayakawa.H et al, nearly 26%of patients with RA had cricoaryetenoid arthritis [86]. Usually the clinically diagnosis is based on direct or indirect laryngoscopy. The finding includes inflammatory changes of the arytenoids with reduced motility. Diagnosis is usually confirmed by CT

In some cases, ankylosis of the cricoarytenoid joint may induce an upper airway obstruction with a characteristic pattern on the flow-volume curve. In these patients with dyspnea, surgery is indicated to treat ankylosis. Some patients are predisposed to obstructive sleep apnea syndrome

Small airway disease:

Small airway disease with physiologic obstruction is common [87]. And these patients usually have non productive cough, dyspnea on exertion or wheezing. The diagnosis is made by HRCT. It usually shows involvement of small airway with centrilobular nodules, heterogenous air trapping and hyperinflation. Pathologically, both fibrosing (obliterative or constrictive bronchiolitis) and cellular (diffuse panbronchiolitis and follicular bronchiolitis) have been well described [88].

"Controlled studies of lung function in patients with RA demonstrate an increased prevalence of chronic airway obstruction (16–38%) [89] and increased bronchial reactivity to methacholine (55%). In a PFT survey of patients with rheumatoid arthritis, airway obstruction was observed in9-37%, even in non-smoking patients [90]. In PFT, constrictive bronchiolitis manifests as severe irreversible airway obstruction with hyperinflation.

Obliterative bronchiolitis:

It is a progressive condition and death from respiratory failure occurs in 2-3years of onset. Histologically the lesion demonstrates bronchiolar

wall destruction with effacement of lumen by granulation tissue and eventual replacement of bronchiolar wall by fibrous tissue. The histologic picture is usually preceded by exudation of inflammatory substrates. The progression of this disease is heterogeneous. It is more in patients having indolent disease. The prevalence of unsuspected OB is uncertain. Patients may benefit from treatment with inhaled corticosteroids and bronchodilators. In 50% of patients the prognosis is poor. PFT shows severe airflow obstruction with reduced DLCO. Pencillamine use has been related to this condition[92].

Follicular bronchiolitis:

Follicular bronchiolitis is characterized by external compression of bronchioles by hyperplastic lymphoid follicles with variable lymphocytic infiltration of the bronchiolar wall. FB is more commonly seen in RA compared to other connective tissue disorders. It is unclear if follicular bronchiolitis predisposes to OB. Isolated FB simulates ILD with reticular or reticulonodular abnormalities on CXR. The PFT abnormality may be Restrictive or obstructive[93]. It is more responsive to corticosteroid therapy.

Lower airway disease:

Bronchiectasis is a common manifestation of RA .Clinically significant bronchiectasis is less frequent and involving 1–5% of Patients with RA. Bronchiectasis is more common in women than in men (male to female ratio of 1:2.8)

In some studies, RA appears at a younger age in patients with bronchiectasis (46vs51 years).Symptoms are identical to other causes of bronchiectasis and include cough, sputum production, frequent episodes of infection, and hemoptysis. The co-existence of RA and bronchiectasis is associated with an alteration of lung function tests and a poor 5-year survival .In most patients (90%), bronchiectasis precedes the development of RA by 25–30years .HRCT studies demonstrate that 20–35% of patients with RA have bronchiectasis (associated with interstitial changes in one-third of the cases)[94].

However, clinically significant disease is much less frequent. Secondary development of bronchiectasis after 7–10years of evolution of RA is possible.

In a case–control study, patients with RA and bronchiectasis were 7.3 times more likely to die than the general population,5.0 times more likely than patients with RA and 2.4 times more likely than patients with bronchiectasis without RA. An increased risk of death within the RA and bronchiectasis group was associated with a history of smoking, moresevere RA and steroid usage. In this study, 60% of the mortality was due to infections and acute respiratory failure.

Bronchiectasis is one of the predisposing factor to lung infections. It also increases the postoperative morbidity in patients with RA. The pathogenesis of bronchiectasis is poorly understood. These patients usually have decreased humoral immunity which may be the reason for increased risk of infection. Some patients with RA have recurrent bronchial infection, lymphedema , pleural effusions and typical nail changes which constitutes yellow nail syndrome.

VASCULAR INVOLVEMENT:

The involvement of lung vasculature is rare in RA. It presents as pulmonary hypertension. Some patients have alveolar hemorrhage

secondary to pulmonary vasculitis. This presentation is correlated with the presence of antineutrophil cytoplasmic antibodies [95].

DRUG INDUCED LUNG DISEASE

Several drugs used for the treatment of RA have been associated with drug-induced lung disease. Methotrexate, goldsalts, D-penicillamine ,and nonsteroidal anti- inflammatory drugs are associated with repiratory adverse effects[97]. Two percent of patients with RA develop an acute respiratory infection requiring hospitalization annually. Pneumonitis as a consequence of treatment with methotrexate is now a frequent feature as the use of this agent increases. "The reported incidence of methotrexate pneumonitis in RA varies from 0.86% to 6.9%[98]" .The risk is maximal in the first year of treatment. Mortality from methotrexate pneumonitis is around 20% in most series[99].

Patients with underlying lung disease and who are smokers are at increased risk for pneumonitis. It is important to diagnose patients with prior predisposing condition so that it may help in alternative treatment regimen. The single most predictive test helpful to identify the risk for pneumonitis is reduced gas transfer ratio. .Patients on methotrexate are at

lesser risk of developing infection than who are not on the drug. The major cause of death is failure to mount immune response in this patients.

A survey from Japan reports an increased risk of acute pneumonitis in leflunomide treated patients with an incidence of 0.5% [100]. In Indian studies, there is no evidence that combination of leflunomide with methotrexate increases the risk of pneumonitis beyond that which methotrexate itself carries.

Infliximab infusions administered for active articular disease have caused acceleration of underlying rheumatoid interstitial lung disease in few patients[101]. Recent data on patients receiving etanercept for RA indicate that this agent can potentiate an acute pneumonitis with ground glass shadowing on HRCT and histological evidence of granulomatous pneumonitis.

This is distinct from Methotrexate pneumonitis and is almost exclusively confined to patients with prior significant lung disease, patients with interstitial damage faring less well than those with airway disease.

CLINICAL STUDIES–PULMONARY INVOLVEMENT IN RA

In a study conducted in 1997 by Cortet-Bernardet, sixty eight patients (54 women,14men), a significant decrease of FEV_1/FVC, FEF25%, FEF50%, FEF75%, FEF25-75%, and TLCO was observed($p<0.05$) and 13.2% of the patients had a small airways involvement defined by a decrease of FEF25-75% below 1.64SD[102]. The most frequent HRCT findings were: bronchiectasis(30.5%), pulmonary nodules (28%), and air trapping(25%).

The patients with small airways involvement had a high frequency of recurrent bronchitis (75%v34%,p=0.05) and bronchiectasis(71% v23%, p=0.019). The patients with bronchiectasis had low values of FEV_1, FVC, FEF25-75%, and TLCO ($p<0.01$). This study suggests a significant association between small airways involvement on PFT and bronchiectasis on HRCT in asymptomatic patients with RA.

In a study conducted in 2004 by Terasakietal, PFT and HRCT were done in 34 patients[103]. Bronchial wall thickening was detected in 85%, small nodules in 71% and bronchial dilatation in 62%. The extent of bronchial wall thickening correlated with MMEF, FEF75 and FEF50.

In another study conducted in 1998 by Perez et al where 50 patients with RA (9malesand41females), included 39 non-smokers and 11 smokers[104]. Airway obstruction (reduced FEV_1/FVC) was found in 18% of patients. Small airway disease, reflected by reduced FEF25-75 was seen in 8% of patients. The airway obstruction and small airway disease correlated well with the presence of bronchiectasis, bronchial wall thickening and with bronchial infection on HRCT.

A study was conducted in 2004 by Doyle et al to determine the prevalence of airway hyperreactivity(AHR) in patients with newly diagnosed rheumatoid arthritis (RA)who had received no disease-modifying anti-rheumatic drugs (DMARD) and to characterize the spectrum of lung diseases identifiable in these patients at the time of presentation[105].The pulmonary abnormalities included two patients with hypoxia (12%), 2withobstruction (12%), 3withrestriction(18%) and 4withAHR(23%). Their data also suggested a strong association between pulmonary diseases in RA and cigarette smoking. Although no single characteristic lung disease such as AHR was identified in patients presenting with RA, the association between pulmonary. Involvement in RA and cigarette smoking is striking.

A study was conducted by Vergnenegre et al in 1997, to assess the percentage of respiratory disorders and airway obstruction in patients with rheumatoid arthritis. They compared lung function test results between patients with rheumatoid arthritis and control subjects with other rheumatological conditions [90].

A prospective case-control study of respiratory symptoms and lung function abnormalities was performed in a series of 100 patients with rheumatoid arthritis. Eighty eight patients with other rheumatological diseases served as controls. Diagnosis of respiratory disorders was based on clinical, radiological and spirometric findings. Airway obstruction was determined from predicted values. The number of symptoms, respiratory disorders (including bronchiectasis) and lung function abnormalities was higher in patients with rheumatoid arthritis than in controls.

In a study conducted by Radoux.V.etal, after excluding smokers, the proportion of airway obstruction in patients with rheumatoid arthritis was 16% (versus0%incontrols), although the patients with rheumatoid arthritis still had more symptoms and respiratory disorders [88].

The Chi-squared test did not identify an relationship between airway obstruction, duration of rheumatoid arthritis and type of treatment. The study concluded that respiratory disorders (including bronchiectasis) and airway obstruction are more frequent among patients with rheumatoid arthritis than in rheumatological controls.

In a study by Fuld et al in 2003, a longitudinal study of pulmonary function in asymptomatic, non-smoking patients with active RA requiring DMARD(19), 134 temporal change in lung function was looked for that would predict subsequent development of PFT abnormality or respiratory symptoms[106]. The prevalence of PFT abnormality was higher than expected when compared with the reference population but there was no significant increase in number over 10 years (8.7%in1990and 8.8% in2000). Reduced DLCO and increased RV/TLC were the only abnormalities to develop over study period. Rates of change of pulmonary function variables were not significantly different from zero.

EVALUATION

RA-ILD is usually when RA patient develops dyspnea, cough, auscultatory crackles, or abnormalities on pulmonary function testing (PFTs) or chest radiograph. The evaluation of suspected RA-ILD typically

includes a combination of laboratory testing, PFTs, imaging, and sometimes bronchoalveolar lavage or lung biopsy. These tests are designed to characterize the presence, pattern, and severity of ILD, and also to exclude differential diagnoses.

A key component of the evaluation is determination of the type of ILD, as all of the histopathologic types of idiopathic interstitial lung disease can occur in the context of RA . Often the cause and type of ILD can be determined by the combination of clinical presentation, PFTs, and HRCT. In a minority of cases, when these features are not typical for a given type of ILD and the patient is symptomatic, fit for surgery, and the biopsy would change the therapeutic approach , characterization of the ILD by lung biopsy is often appropriate .

It is important to determine whether the patient is experiencing a first presentation of new interstitial disease, an exacerbation of previously unknown interstitial disease (usually UIP pattern), or one of these possibilities combined with a superimposed comorbid disease not directly due to RA. Investigations evaluating the various pulmonary manifestations

of RA are designed to exclude the possibility that another lung disease or extra-pulmonary process is etiologic, such as:

- Infection
- Drug-induced lung
- Hypersensitivity pneumonitis due to inhalational
- A new or intercurrent ILD, such as acute interstitial pneumonitis or vasculitis, if symptoms are rapidly progressive
- Heart failure, pulmonary embolism, cancer, or recurrent gastroesophageal aspiration

Laboratory testing —

For patients with (or without) RA who present with diffuse lung disease, we generally obtain a complete cell count and differential to look for leukocytosis (infection), leukopenia (immune suppression due to medication), or eosinophilia (possible drug reaction). A serum natriuretic peptide level is measured to screen for heart failure or pulmonary hypertension. Most patients have already had serologic testing for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA), but full assessment of other autoantibodies should be performed, including antinuclear antibodies and anti-double stranded DNA antibodies,

and also cryoglobulins to assess for co-existent rheumatic disease that may be contributory in the appropriate clinical setting, such as when purpura, Raynaud phenomenon, skin ulcers, or renal disease are present.

Rheumatoid factor may be present in high titer in patients with ILD . ACPA positivity also correlates with the presence of RA-ILD and higher titers of ACPA may be associated with more severe ILD .

While the sedimentation rate (ESR) and C-reactive protein (CRP) correlate with activity of RA joint disease, their role in the evaluation of lung disease is unclear.

Pulmonary function tests :

Complete lung function testing (spirometry, lung volumes, diffusing capacity) and pulse oximetry are obtained in all patients with suspected ILD to assess the pattern, severity, and progression of respiratory impairment.

Abnormalities associated with ILD include reductions in lung volumes and diffusing capacity for carbon monoxide , oxygen desaturation during exercise, and in late disease, resting hypoxemia. In a study of 81 patients with recent onset rheumatoid arthritis, for example, 33 percent had a DLCO

<80 percent of predicted, while only 14 percent had symptoms . When assessing changes over time, changes that are considered clinically important include a decrease in forced vital capacity of ≥10 percent or a decrease in DLCO of ≥15 percent.

Among patients with RA, restrictive abnormalities on pulmonary function tests are common even in the absence of symptoms and may reflect poor muscle strength or kyphosis due to osteoporosis rather than ILD. The association of restrictive abnormalities and evidence of abnormal gas exchange (eg, reduced DLCO, low pulse oxygen saturation) favor the diagnosis of ILD.

Arterial blood gases are obtained to corroborate abnormal pulse oxygen saturation or DLCO findings.

Imaging studies —

In patients with RA, a chest radiograph is typically obtained to assess complaints of dyspnea or abnormal findings on lung examination. Further imaging depends on the chest radiograph findings and severity of symptoms.

- **Chest radiograph** –

The chest radiograph may be normal in patients with early or mild RA-ILD. When abnormal, potential findings include bibasilar ground glass

opacities, reticular and nodular opacities, and honeycombing. Late in the course of the disease, changes suggestive of pulmonary hypertension (eg, enlargement of central pulmonary arteries, attenuation of peripheral vessels) may be detectable

- **High resolution computed tomography** –

High resolution computed tomography (HRCT) is obtained in almost all patients with symptoms, PFT findings, or chest radiograph abnormalities suggestive of diffuse parenchymal disease. Both prone and supine views are obtained to avoid misinterpretation of gravity-induced opacities in dependent areas. HRCT detects abnormalities earlier than chest radiography and may reveal a range of parenchymal abnormalities . In one study of 20 non-smoking patients with RA and normal chest radiographs, five patients had basilar bronchiectasis and one had mild ILD by HRCT . In a review of 84 patients with longstanding RA, 29 percent of asymptomatic and 69 percent of symptomatic patients had abnormalities on HRCT. These findings included bronchiectasis or bronchiolectasis in the absence of fibrosis (19 percent); ground glass attenuation (14 percent); nonseptal linear attenuation (18 percent); and honeycombing (10 percent). In general, the HRCT findings accurately predict the pathologic findingsHRCT can

distinguish a predominantly ground glass pattern from reticular changes and honeycombing, which is helpful in differentiating among the various types of ILD. As examples:

•Ground glass opacification is consistent nonspecific interstitial pneumonia (NSIP), acute interstitial pneumonia, and desquamative interstitial pneumonia (DIP).

•Reticular changes, traction bronchiectasis, and honeycombing are more typical of usual interstitial pneumonia (UIP) . Infrequently, however, the HRCT may suggest UIP, but NSIP will be identified by biopsy •Persistent areas of subpleural consolidation are more suggestive of organizing pneumonia [7].

Review of previously performed CT images, including abdominal CTs with views that include the lung bases, may identify a pre-existing ILD. In addition, review of older images can help determine the rate of progression of ILD and whether the timing of changes in CT findings over time correlates with symptoms or medication usage.

●**Nuclear imaging** –

Nuclear imaging with gallium and technetium-99m diethylene triamine penta-acetic acid (Tc-99m DTPA) may be abnormal in RA-ILD. However, the role of these studies in diagnosis or prognosis of RA-ILD has not been defined.

Bronchoalveolar lavage —

The main role for bronchoalveolar lavage (BAL) in patients with an acute onset of respiratory symptoms or fever and radiographic abnormalities is to exclude diffuse lung diseases other than RA-ILD, such as acute eosinophilic pneumonia, alveolar hemorrhage, malignancy, or opportunistic or atypical infection. BAL is frequently abnormal in patients with RA-ILD, but the findings are nonspecific.

Abnormalities in cellular constituents and mediators found on BAL are not useful for differentiating among the types of RA-ILD or predicting prognosis or response to therapy. As a result, BAL is not considered to be a routine part of the diagnostic approach to RA-ILD. The following BAL findings have been reported from research studies:

●In patients with clinical evidence of RA-ILD, total cells, neutrophils, and occasionally eosinophils are elevated .

●In the absence of symptoms, lymphocytosis is more common . This finding may be associated with a better prognosis, as evidenced by the subclinical nature of the lung disease.

●Increases in the production of tumor necrosis factor (TNF) alpha by macrophages and the levels of superoxide anion, fibronectin, and collagenase activity in BAL have been noted in patients with RA-ILD .

Lung biopsy —

As HRCT patterns have been found to correlate reasonably closely with ILD histopathologic patterns, lung biopsy is rarely required in most patients with RA-ILD. However, when the results of the above evaluation do not allow the clinician to make a confident diagnosis of a given type of ILD (eg, UIP) and the patient's lung disease is clinically significant and/or progressing, lung biopsy with careful examination of lung tissue is appropriate. A transbronchial biopsy obtained via flexible

bronchoscopy is usually inadequate for diagnosis, so lung biopsy is typically performed by either video-assisted thoracoscopy (VATS) or open thoracotomy. The decision about whether a lung biopsy should be performed should be made on a case-by-case basis, taking into account the patient's clinical condition and the impact of the results on the patient's management. As an example, lung biopsy may be warranted in younger patients in whom lung transplantation might be considered eventually.

Serum markers —

No serum markers have demonstrated clinical utility for the diagnosis of RA-associated ILD, although some may be promising. Increased serum concentrations of KL-6, a glycoprotein found predominantly on type II pneumocytes and alveolar macrophages, have been reported in patients with interstitial pneumonia . As an example, one study assessed the potential role of serum KL-6 for the diagnosis of ILD associated with systemic inflammatory disorders in 57 patients, 22 of whom had known ILD . Patients with ILD had significantly higher KL-6 values than those without lung disease, with the sensitivity and specificity ILD estimated at 61 and 99 percent, respectively, in this selected population. Measurement of serum KL-6 remains a research tool at present, but may become clinically useful in the future if the high specificity of the test is confirmed.

Another report noted that serum anti-interleukin-1-alpha antibody titers were significantly higher in patients with RA and ILD, in comparison to patients with RA, but not ILD, and to controls. Higher titers were associated with higher serum lactic dehydrogenase (LDH) concentrations and larger alveolar to arterial oxygen gradients .

In a case series (58 patients with RA-ILD; 27 with RA but no ILD), serum antibodies to citrullinated Hsp90 appeared specific (>95 percent), although not sensitive for RA-ILD . Anti-citrullinated Hsp90 antibodies were not found in 41 patients with mixed connective tissue disease or 33 patients with idiopathic pulmonary fibrosis, further suggesting specificity. The role of these autoantibodies to citrullinated-Hsp90 in identifying patients with RA-associated ILD needs validation in other groups of patients with RA. In a separate study, a stronger association was observed between the number of anti-citrullinated peptide antibodies (ACPA) and radiographic usual interstitial pneumonia than with non-specific interstitial pneumonia . If confirmed this would be a very useful test to help distinguish between these two entities.

DIAGNOSIS —

The diagnosis of RA-ILD is generally based on the combination of compatible clinical features, pulmonary function testing (eg, restrictive changes and a gas transfer abnormality), and high resolution computed tomography (HRCT) findings (eg, reticular, ground glass, or consolidative changes), and also exclusion of other processes, such as infection, drug-induced pulmonary toxicity, and malignancy.

Determination of the underlying pattern of RA-ILD may be based on a typical HRCT pattern or on lung biopsy findings.

DIFFERENTIAL DIAGNOSIS —

In patients with RA, the differential diagnosis of diffuse lung disease includes drug-induced lung toxicity, opportunistic infection, heart failure, recurrent aspiration, malignancy, and other inflammatory causes of ILD. In addition, patients presenting with new respiratory symptoms with evidence of ILD may have an exacerbation of previously unknown ILD. In the latter situation, obtaining old computed tomography images, even if performed for an abdominal problem, may provide clues to pre-existing disease.

● **Drug-induced lung toxicity** –

Drug-induced lung toxicity has been associated with most of the medications used to treat RA, including the nonsteroidal anti-inflammatory drugs (NSAIDs) , methotrexate , leflunamide , gold, penicillinamine, and biologic agents (eg, tumor necrosis factor inhibitors tocilizumab , rituximab) . Toxicity has rarely been reported with anakindra and not with abatacept. Also, no reports of drug-induced ILD have been published since approval of the Janus kinase (JAK) enzyme inhibitor tofacinib for use in RA. An essential step in the evaluation of possible drug-induced lung toxicity is to stop any implicated medication(s) and observe for improvement over the next few days to weeks.

Development of a sarcoid-like reaction in the lungs has been reported with infliximab , adalimumab , entanarcept and appears to be a class effect of anti-tumor necrosis factor-alpha (anti-TNF-alpha) agents .

Patients may present with dry cough, night sweats, and weight loss . Onset of disease ranges from 1 to 50 months after initiation of the anti-TNF agent . Sarcoid-like granulomas have also been reported in the skin, lymph nodes, and bone marrow in association with anti-TNF-alpha agents. In one

series, the serum angiotensin converting enzyme level was elevated in 48 percent . Cessation of the anti-TNF-alpha agent generally leads to resolution of the granulomas over several months . Recurrences have been reported when the same anti-TNF-alpha agent is resumed, but appears less common when an alternate agent is used .

● **Opportunistic infection** –

Opportunistic infections are well-known complications of immunosuppressive therapies used to treat RA. The diagnosis of opportunistic infection typically requires special stains and culture of induced sputum and/or bronchoalveolar lavage specimens.

Pneumocystis (jirovecii) pneumonia (PCP) is associated with all of the immunosuppressive agents, particularly when the patient is receiving a glucocorticoid dose equivalent to ≥20 mg of prednisonedaily for one month or longer in addition to a second immunosuppressive agent or taking an anti-TNF-alpha agent in combination with other intensive immunosuppression. PCP should be in the differential of new, recent onset dyspnea, fever, and diffuse of patchy radiographic disease.

Anti-TNF-alpha agents also increase the risk for new and reactivation of latent fungal infections, such as histoplasmosis, coccidioidomycosis, cryptococcosis, and other invasive fungal infections.

Mycobacterial disease (both tuberculous and nontuberculous) is well-described complication of anti-TNF-alpha agents.

● **Hypersensitivity pneumonitis** –

The clinical, imaging, and histopathologic characteristics of chronic hypersensitivity pneumonitis are similar to those of the UIP pattern of RA-ILD. The radiographic findings typical of subacute hypersensitivity pneumonitis (eg, diffuse micronodules, ground glass attenuation) are also seen in some patients with RA and organizing pneumonia.

● **Other causes** –

Heart failure is generally excluded based on physical examination, natriuretic peptide measurement, and echocardiogram. Recurrent aspiration typically affects the lower lobes; swallowing difficulties provide a clue to the diagnosis, although they are not always present.

The optimal treatment for RA-ILD has not been determined, but generally parallels the treatments that have been used for the underlying type of interstitial pneumonia, whether that pattern is diagnosed by lung biopsy or presumed based on clinical presentation and high resolution computed tomography (HRCT). Certainly patients who are current cigarette smokers should be encouraged to stop smoking. Case series and clinical experience suggest a benefit to systemic glucocorticoids and immunosuppressive agents in selected patients .

As with the idiopathic interstitial pneumonias, the decision to treat the various histopathologic forms of RA-ILD needs to weigh prognosis, likelihood of response to therapy, and potential benefits of early therapy (ie, before fibrosis is established) against the potentially significant adverse effects of treatment (eg, uncontrolled diabetes, immunosuppression, osteoporosis). Abnormalities in any single pulmonary function test are common in patients with RA. Thus, the diagnosis of clinically significant disease that warrants further monitoring or treatment is based upon the severity of impairment, rate of progression, and pattern of abnormalities identified by the investigations described above, rather than results of a single test.

As a way to guide treatment and monitoring strategies, a newer approach used in guidelines for idiopathic interstitial pneumonias has been to categorize the disease behavior as self-limited, reversible, stable, progressive, or irreversible, with or without the potential for long-term stabilization with therapy. This means that predictors of survival, such as a low diffusing capacity and extensive fibrosis on the HRCT, linked with observed rate of progression may better guide treatment in the face of infrequent pathological confirmation, heterogeneous outcomes, and little data to guide treatment other than clinical behavior

Patients who can be monitored without specific treatment —

Asymptomatic patients and those with mild RA-ILD are monitored with clinical assessment, pulmonary function tests (PFTs), and a chest radiograph at six to twelve month intervals, or sooner if symptoms worsen. Similarly, patients with a usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF) pattern and stable disease by symptoms, PFTs, and HRCT are monitored without specific therapy (other than treatment of their articular disease), as no therapy has been shown to improve this type of lung disease. Typically, these latter patients are older, and their RA-ILD is unlikely to respond to glucocorticoids or immunosuppressive therapies.

Therapy of their joint disease continues as indicated, although any drugs that are associated with lung toxicity are discontinued.

Indications for treatment —

Features that suggest that treatment of RA-ILD is likely to be beneficial include younger age, histopathologic patterns other than UIP, and worsening of symptoms, PFTs, or HRCT over the preceding three to six months. The decision to commence therapy is also influenced by the presence of comorbid disease that might increase the risk of adverse effects (eg, diabetes mellitus, osteoporosis).

Some clinicians would also treat selected patients with a radiographic UIP pattern of RA-ILD who are young, have a shorter duration of ILD, and deteriorating lung function, but no significant comorbid problems. This approach was addressed in a retrospective study of 144 patients with RA-UIP of whom 41 percent received immunosuppressive treatment due to poor initial lung function or ILD progression.

After a median follow up of 33 months, 50 percent of those treated had improved or remained stable, despite an expectation that these patients would be most likely to progress. Furthermore, there was no difference in

outcome between the treated and untreated groups, despite worse initial lung function in the treatment group. This study, while not randomized, would suggest that the outlook with treatment is better in RA-UIP than IPF or that the clinical diagnosis of RA-UIP is not accurate and may include patients with RA-NSIP, shown to have a better prognosis and response to treatment. Thus, treatment with a goal of slowing disease progression may reasonably be considered in such patients, while awaiting further data.

Patients with the organizing pneumonia, nonspecific interstitial pneumonia, and lymphocytic interstitial pneumonia histopathologic types of RA-ILD are believed to be likely to respond to glucocorticoid/ immune-suppressive therapy based on experience with the idiopathic forms of these ILDs and on clinical reports.

Initiation of glucocorticoid therapy —

Glucocorticoid therapy produces variable subjective and objective improvement in the treatment of RA-ILD, although some of the reported variability in response may be due to a lack of precision in determining the histopathologic subtype . As with the idiopathic interstitial pneumonias, the results may depend upon the relative proportions of inflammatory or fibrotic changes within the pulmonary parenchyma .

For symptomatic patients with RA-ILD, evidence of progressive respiratory impairment, an amenable histopathologic type (ie, non-UIP based on HRCT or biopsy), and no evidence of lung infection, we suggest initiating therapy with oral prednisone at a dose of 0.5 mg/kg per day, based on ideal body weight as a single morning dose . A maximum dose of 60 mg/day should not be exceeded, as there is no clear benefit but significant risk above this level. If a response is going to occur, it is usually seen within one to three months. The prednisone dose should be slowly reduced to a maintenance dose of 10 mg/day once a response occurs, using symptomatic response and pulmonary function tests to monitor disease activity.

In severe, rapidly progressive disease, after excluding infection, glucocorticoids are administered intravenously, as described for fulminant disease.

Failure to respond to systemic glucocorticoids —

Patients who fail to respond to glucocorticoids alone may benefit from addition of an immunosuppressive agent, such as mycophenolate, azathioprine, or cyclophosphamide, although evidence in favor of this practice is limited to case series and clinical experience. After

excluding infection or drug-toxicity as a cause for the failure to respond, one of these agents is added to the ongoing prednisonedose; as examples, azathioprine (eg, 3 mg/kg orally up to 200 mg/day), mycophenolate mofetil (eg, 250 mg given twice a day initially with a target dose of 1.5 to 2 g/day), or cyclophosphamide (eg, 100 to 120 mg orally/day as a single daily dose). Given the toxicity of cyclophosphamide, use of this drug is generally reserved for more severe or refractory disease. The dosing and potential adverse effects of these agents are discussed separately.

Evidence in favor of mycophenolate comes from a series of 125 patients with connective tissue-related ILD, including 18 with rheumatoid arthritis . Mycophenolate mofetil was associated with modest improvements in forced vital capacity and diffusing capacity and reductions in theprednisone dose (mean decrease among RA patients 20 mg). The discontinuation rate for adverse effects (gastrointestinal intolerance, hepatic transaminase elevation, cytopenia, and nonspecific symptoms) was under 10 percent.

Hydroxychloroquine was used successfully in combination with mycophenolate in a small case series, but is almost never used as a single agent. It is not known whether pirfenidone and N-acetyl cysteine,

which may be of benefit in idiopathic pulmonary fibrosis, have a role in the management of RA-ILD with a UIP pattern.

We avoid methotrexate in patients with RA-ILD due to the risk of lung toxicity from methotrexate. In a series of 64 patients with RA and preclinical ILD, progressive ILD was more frequent in those treated with methotrexate than other medications (eg, prednoisone, leflunomide, hydroxychloroquine, tumor necrosis factor [TNF]-alpha inhibitors or nonsteroidal anti-inflammatory drugs), suggesting that methotrexate is not optimal in this setting .

Inability to taper glucocorticoids or intolerance of adverse effects —

For patients who are unable to taper the glucocorticoid dose or have intolerable adverse effects, addition of an immunosuppressive agent may enable successful tapering of the glucocorticoids. Although published experience in RA-ILD is limited, this approach is used for several of the idiopathic interstitial lung diseases]. As an example, mycophenolate or azathioprine can be added at the doses described above, while continuing prednisone at as low a dose as possible (eg, 0.2 to 0.25 mg/kg per day, or ≤10 to 15 mg daily).

Fulminant disease —

For the minority of patients who develop rapidly progressive acute interstitial lung disease or organizing pneumonia as a complication of RA, after excluding infection and drug-induced lung toxicity, we follow treatment regimens for the particular type of ILD (eg, acute interstitial pneumonitis, organizing pneumonia). As these patients typically have impending or actual respiratory failure, treatment typically includes high-dose systemic glucocorticoids (eg,methylprednisolone 1 to 2 g per day given intravenously as a pulse or in divided doses for three to five days). An immunosuppressive agent may be added at the same time, such as cyclophosphamide or azathioprine, although evidence in favor of this practice is lacking.

Monitoring —

For patients who are being treated with systemic glucocorticoids or other immunosuppressive therapy, monitoring for an objective response to treatment is generally performed at one to three month intervals with clinical assessment, serial chest radiographs or high resolution computed tomography, and PFTs (eg, spirometry, lung volumes, diffusing capacity [DLCO], six minute walk test with monitoring of oxygen saturation).

Monitoring for adverse effects of therapy for RA-ILD is essential. As examples:

● **Monitoring for hematologic and hepatic toxicity** –

Close hematologic monitoring is needed with all of the immunosuppressive agents (eg, monthly initially and then every three months). Toxicity of azathioprine is partly related to deficiency in the enzyme thiopurine methyltransferase (TPMT), and analysis of the TPMT gene prior to the administration of azathioprine may help predict those individuals at risk for severe toxicity. In addition to hematologic monitoring, liver function tests are obtained monthly at first and then every three months. The pharmacology and adverse effects of azathioprine are discussed separately. With cyclophosphamide, liver function monitoring follows a similar frequency, while renal function is assessed every two to four weeks. Additional details about the administration and monitoring of these agents are provided in the table and separately .

● **Drug-induced pulmonary toxicity** –

Almost all of the disease modifying antirheumatic drugs (DMARDs) and biologic therapies have been associated with lung toxicity,

so clinicians should keep this possibility in mind should unexpected worsening of ILD occur during therapy.

An important clinical question is whether drugs known to cause lung toxicity should be avoided in patients with underlying lung abnormalities due to concern about potential exacerbation. A systematic review has shown the overall risk of a drug reaction is low (1 percent), although if a reaction occurs, it often has a high mortality . Potentially life-benefiting antirheumatic medications should not necessarily be withheld for what appears to be an uncommon side effect, but such patients do require ongoing monitoring for worsening respiratory symptoms or function.

- **Infection** –

A variety of serious infections have been described with use of these immunosuppressive therapies. Prophylaxis against PCP may be warranted for some of the above treatment regimens. While the low doses of prednisone and methotrexate typically used in RA do not warrant prophylaxis, the combination of a glucocorticoid dose equivalent to ≥20 mg of prednisone daily for one month or longer and a second immunosuppressive agent or the combination of an anti-tumor necrosis factor-alpha agent with other intensive immunosuppression may warrant prophylaxis.

Vaccination with the influenza vaccine should be provided annually to all patents with rheumatoid arthritis. Administration of the polysaccharide pneumococcal vaccine is recommended in all adults with chronic lung disease. In addition, a second dose of the polysaccharide vaccine five years after the first is suggested in patients receiving immunosuppressive therapies. The pneumococcal conjugate vaccine is also suggested in such patients.

- **Prevention of osteoporosis** –

For patients on long-term oral glucocorticoids, osteoporosis is a concern, and oral calcium and vitamin D supplementation are recommended (eg, daily calcium 1200 mg and vitamin D 800 international units) for prophylaxis. Depending on the patient's age and baseline bone density, pharmacologic therapy (eg, bisphosphonates) may also be indicated. The prevention and treatment of osteoporosis are discussed separately.

- **Cyclophosphamide and hemorrhagic cystitis** –

A high fluid intake is encouraged to prevent hemorrhagic cystitis with cyclophosphamide.

● **Malignancy** –

Patients on long-term therapy with cytotoxic medications are at risk of developing malignancy, particularly skin, cervical, and, withcyclophosphamide, bladder cancer. Thus, patients should be educated about avoidance of the sun and use of sunblock, and women should receive regular mammograms and cervical Papanicolaou smears.

Lung transplantation and novel therapies —

Lung transplantation may be an option in end-stage RA-ILD. Among ten patients with RA-ILD who underwent lung transplantation, survival at one year was comparable to lung transplantation recipients with idiopathic pulmonary fibrosis, 67 and 69 percent, respectively . A modest improvement in quality of life with respect to respiratory symptoms was also noted. Side effects of the therapy for RA (eg, osteoporosis) may be a contraindication; other extrapulmonary disease manifestations may also complicate transplantation.

The potential role of newer therapies for RA (eg, rituximab, anti-TNF alpha regimens, abatacept, tocilizumab) in ameliorating RA-ILD is awaited with interest . In a case series, rituximab was administered in an open-label fashion to 10 patients with progressive RA-ILD of the UIP or NSIP types . Lung disease appeared to stabilize in four and improve in one, although three patients withdrew due to adverse effects (eg, infusion

reactions, heart failure, possible pneumonia). Any potential benefit of anti-TNF-alpha therapy should be viewed in the context of several cases of rapid, occasionally fatal progression of lung disease in patients with RA-associated ILD treated with anti-TNF therapy . Abatacept and tocilizumab have had a beneficial effect in case reports, although tocilizumab has also been reported to have adverse lung effects as discussed above.

PROGNOSIS —

The prognosis of RA-ILD depends on the histopathologic subtype . For many patients with RA-ILD, the pulmonary abnormalities do not progress and may remain subclinical. The effect of presumed histopathologic subtype was assessed in a retrospective review of 144 patients with RA-ILD, using high resolution computed tomography and, in a smaller number of patients, pathology . The poorest prognosis at five years was in those with diffuse alveolar damage (DAD) (20 percent) and usual interstitial pneumonia (37 percent), while a better prognosis was found for organizing pneumonia (60 percent), bronchiectasis (87 percent), bronchiolitis (89 percent), and nonspecific interstitial pneumonia (94 percent). In a separate retrospective review of 84 patients with RA-UIP who were monitored for 33 months, respiratory abnormalities remained stable in approximately 50 percent, progressed in 30 percent, and deteriorated

rapidly in 17 percent. Importantly, the stable group remained stable for a median of 45 months .

Data from the United States National Center for Health Statistics suggest that overall mortality rate from rheumatoid arthritis decreased between the years 1988 and 2004 (from 52.4 to 45.3 per 10^6 in women and 23.3 to 15.3 per 10^6 in men) . However, during that interval mortality rates due to RA-ILD increased 28 percent in women (from 2.4 to 3.1 per $10^{6)}$ and declined 12 percent in men (from 1.7 to 1.5 per 10^6). Overall, RA-ILD was associated with a slightly shorter survival (approximately three years) compared with RA without ILD.

The histopathologic similarity of RA-ILD and IPF has led to studies comparing their respective outcomes, but these studies have yielded conflicting results. In one case-control study comparing 18 patients with RA-ILD versus 18 patients with IPF, the median survival was greater for patients with RA-ILD (60 versus 27 months) . In a separate series of 86 patients with RA-ILD and 872 with IPF, survival was similar between the two groups .

A diffusion capacity less than 55 percent is an indicator of a poor prognosis .

In one study, 80 percent of patients whose disease progressed had a diffusion capacity less than 54 percent (ie, 80 percent sensitivity) and 93 percent of patients whose disease did not progress had a diffusion capacity greater than 54 percent (ie, 93 percent specificity). It seems likely that prognosis is also related to the histopathologic pattern, although data are lacking.

MATERIALS AND METHODS

- **STUDY POPULATION:**

  This study is to be conducted in known RA adult patients attending Medicine / Rheumatology OPD.

- **INCLUSION IN CRITERIA:**

  Those patients satisfying 2010 ACR / EULAR criteria for classification of RA were included in the study.

- **STUDY DESIGN:**

  50 adult rheumatoid arthritis patients (25 naïve and 25 on treatment) attending Medicine / Rheumatology OPD in Madurai Medical College were included in the study.

STUDY PROTOCOL

- **DESIGN OF STUDY:**

  Cross sectional study

- **PERIOD OF STUDY:**

  4 months (JULY 2014 TO OCTOBER 2014)

- **COLLABORATING DEPARTMENTS:** Department of

  Medicine, Department of

  Thoracic medicine Department of

  Rheumatology Department of

  Radiology,

- **ETHICAL CLEARANCE:** Obtained

- **CONSENT:** Individual written and informed consent.

- **ANALYSIS:** STATISTICAL ANALYSIS

- **CONFLICT OF INTEREST**: NIL

- **FINANCIAL SUPPORT:** NIL

- **PARTICIPANTS:**

50 adult patients attended Medicine / Rheumatology OPD of Govt. Rajaji Hospital, Madurai

RESULTS

TABLE-1: SEX DISTRIBUTION OF PATIENTS WITH RA

	Male	Female
Treatment naive	4	21
On treatment	12	13

50 patients with rheumatoid arthritis who presented to Madurai medical college, Madurai over a period of 4 months were included the study. This included 34 females and 15 males [M: F ratio 1:2].

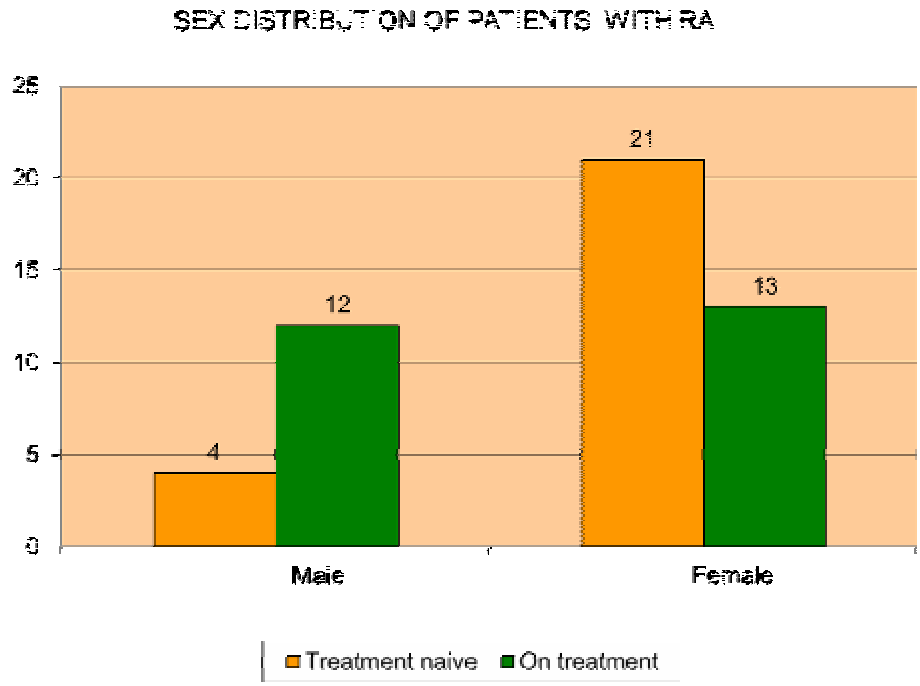


TABLE-:2

AGE DISTRIBUTION OF PATIENTS IN TREATMENT NAIVE

Age	Frequency	Percent
20 – 29 yrs	3	12
30 – 39 yrs	2	8
40 – 49 yrs	7	28
50 – 59 yrs	10	40
60 – 69 yrs	2	8
70 – 79 yrs	1	4
Total	25	100

AGE DISTRIBUTION OF PATIENTS ON TREATMENT

Age	Frequency	Percent
20-29yrs	1	4
30-39yrs	5	20
40-49yrs	5	20
50-59yrs	12	48
60-69yrs	2	8
70-79yrs	0	0
Total	25	100

	N	Mean	SD	Minimum	Maximum
Age	25	47.56	10.91	23	65

	N	MEAN	S.D	Minimum	Maximum
Age	25	47.64	11.3	25	70

4 patients (7.5%) patients were aged between 20 -29 years

7 patients were aged between 30-39 years

12 patients were aged between 40 – 49 years

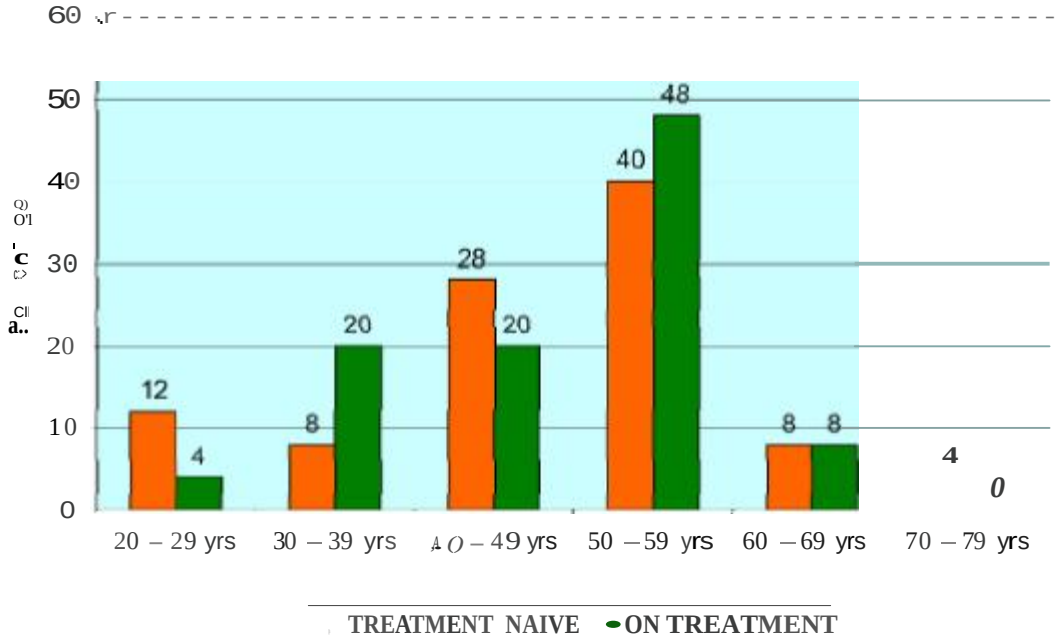
22 patients were aged between 50 – 59 years

4 patients were aged between 60-69 years

1 patients was present in the age group between 70 – 79 years

Mean age was 47 years

AGE DISTRIBUT ION **AND COMPARISON**

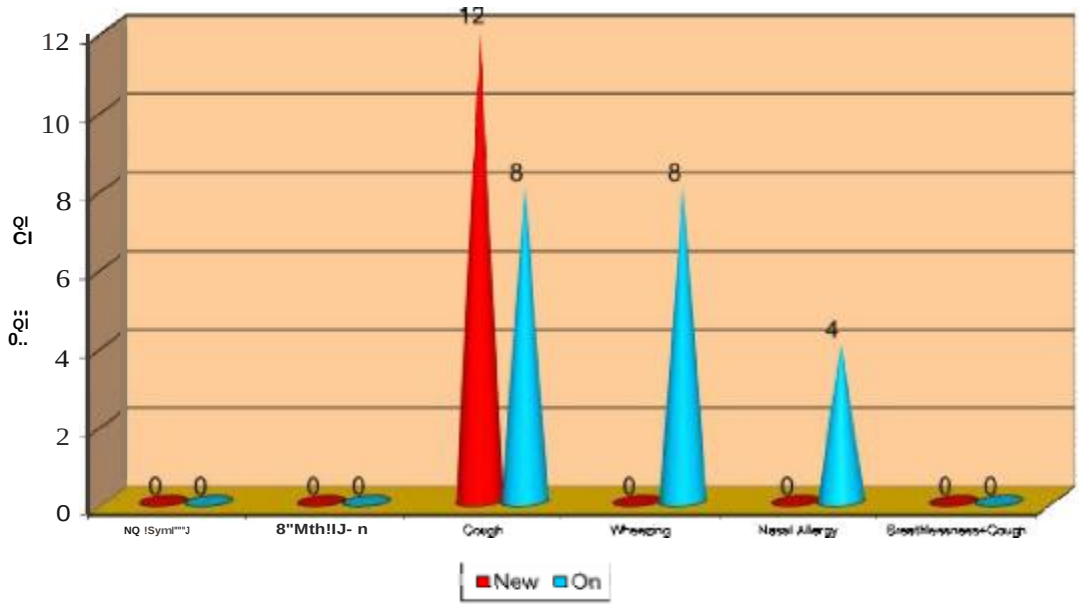


TABLE–3
INCIDENCE OF RESPIRATORY SYMPTOMS IN PATIENTS WITH RA

Respiratory Symptoms	Frequency		Percent	
	new	On ℟	New	On ℟
No Symptoms	22	20	88%	80%
Breathlessness	-	-	-	-
Cough	3	2	12%	8%
Wheezing	-	2	-	8%
NasalAllergy	-	1	-	4%
Breathlessness+Cough	-	-	-	-
Total	25	25	100	100

8 patients had respiratory symptoms. The symptoms included dry cough 5 (10%) patients, wheezing 2 (4%), and nasal allergy 1 (2%).

INCIDENCE OF RESPIRATORY SYMPTOMS IN PATIENTS WITH RA



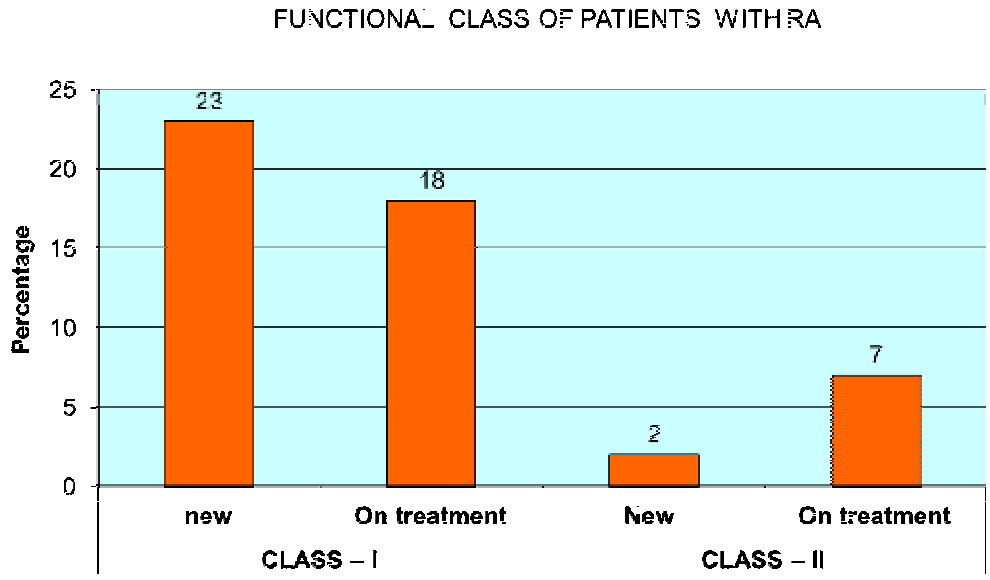
TABLE–4

FUNCTIONAL CLASS OF PATIENTS WITH RA

CLASS–I		CLASS–II	
New	On Treatment	New	On treatment
23	18	2	7

41 patients were in functional class I

9 patients were in functional class II, none of the patients included in the study were in functional class 3 and 4.



TABLE– 5

DURATION OF TREATMENT OF METHOTREXATE IN PATIENTS WITH RA

On methotrexate	Frequency	percent
3-6 years	13	45%
More than 6 years	12	55%
total	25	100%

Out of 25 patients 13 patients were on treatment for 3 -6 years and 12 were on treatment for more than 6 years.

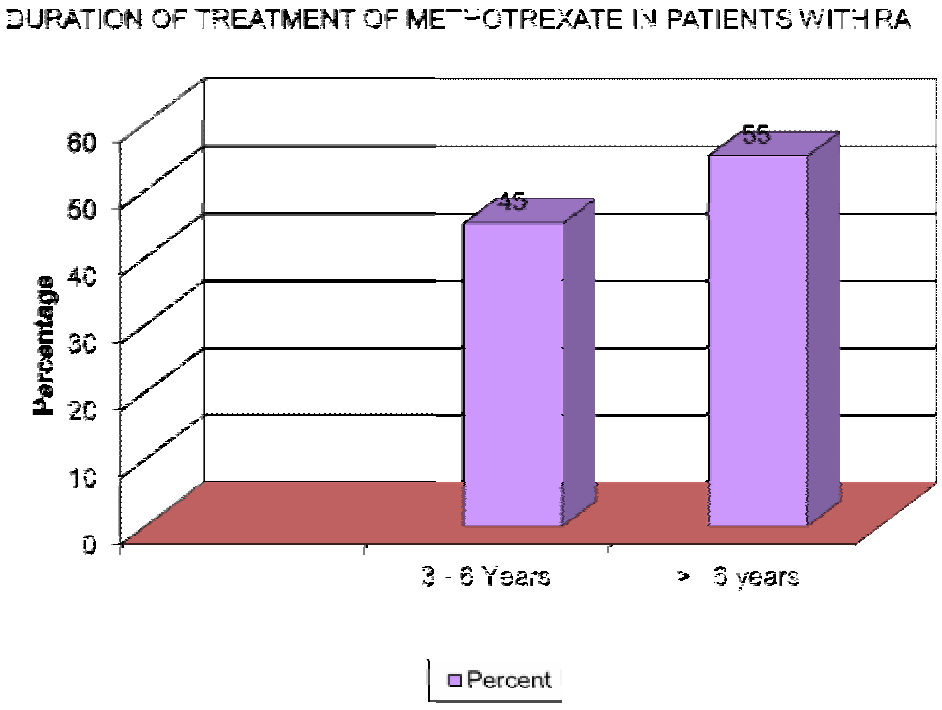


TABLE-6:
PFT ABNORMALITIES IN PATIENTS WITH RA TYPE AND SEVERITY

PFT Finding	Frequency		Percent	
	New	On treatment	New	On treatment
Obstruction	4	5	16%	20%
Restriction	10	11	40%	44%
Normal	11	9	44%	36%
Total	25	25	100%	100%

In Newly diagnosed group 56 % had abnormal PFT this included 4(16%) obstructive, 10 (40 %) restrictive pattern

Among the obstruction 2 (8%) were mild, 2(8%) moderate.

Among the restriction 9(36%) were mild, 1(4%) moderate

On treatment group:

16 patients (64%) had abnormal PFT this included 5 (20%) obstructive, 11 (44%) restrictive

Among obstructive – 4 (16%) were mild, 1 (4%) severe.

Among restrictive – 8 (32%) were mild, 2 (8%) were moderate, 1 (4%) severe.

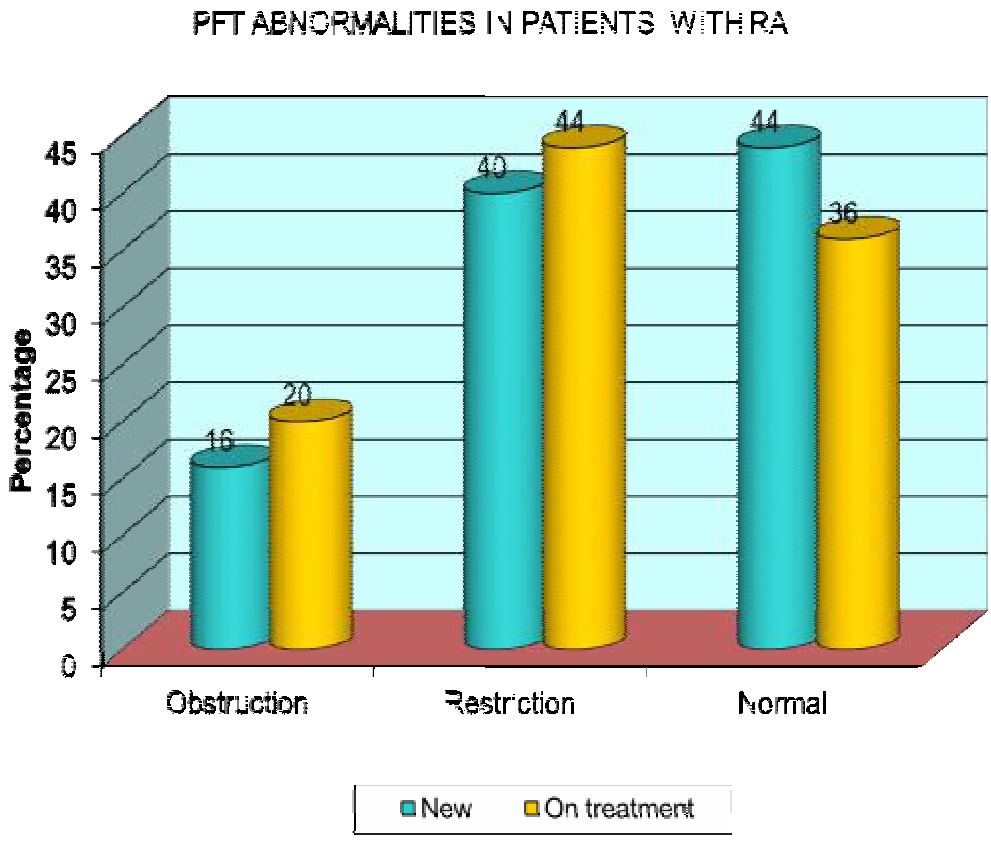


TABLE 7

GENDER DISTRIBUTION OF PFT FINDINGS

PFT Finding	Gender				Total	
	Male		Female			
	I	II	I	II	I	II
Obstruction	2	5	2	-	4	9
	8%	20%	8	-	16%	20%
Restriction	2	4	8	7	10	11
	8%	16%	32%	28%	40%	44%
Normal	0	2	11	7	11	9
	0%	8%	44%	28%	44%	36%
Total	4	11	21	14	25	25
	16%	44%	84%	56%	100%	100%

Chi-SquareValue	df	'p'value
0.107	1	0.744

Treatment naïve group: 2 (8%) patients out of 4 patients with obstruction were males and 2 (8%) were females .2 (8%) out of 10 patients with restrictive were males and 8 (24%) patients were females and 11 patients had normal PFT.

On treatment group:

5 (20%) patients out 5 were male had obstructive pattern

4 (16%) patients out of 11 with restrictive were male , 7 (28%) were female.

2 (8%) out of 9 patients with normal PFT were male , 7 (28%)were female.

More patients among females had restriction were compared to males this is statistically significant P value 0.0001.

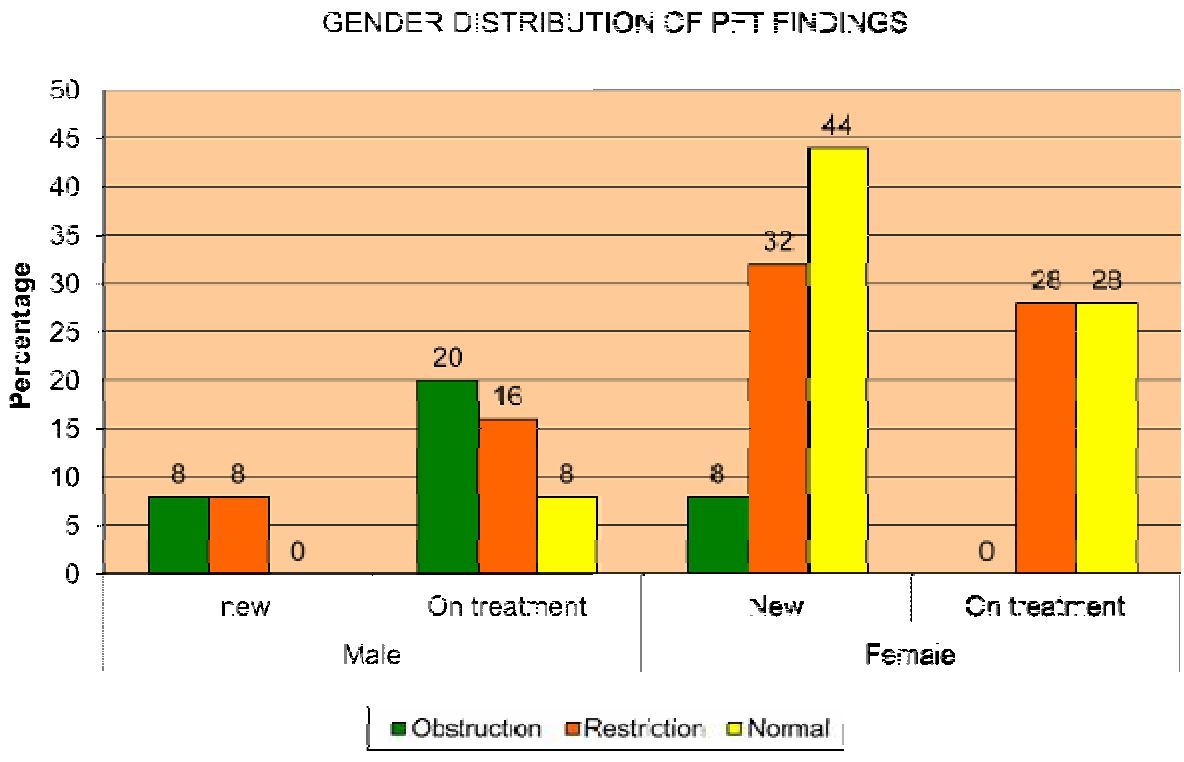


TABLE-8
AGE WISE DISTRIBUTION OF PFT FINDINGS

PFT	Age in Years											
	20-29 yrs		30-39 yrs		40-49 yrs		50-59 yrs		60-69 yrs		70-79 yrs	
	I	II	I	II	I	II	I	II	I	II	I	II
Obstruction	-	-	-	-	2	-	2	4	-	1	-	-
	-	-	-	-	8%	-	8%	16%	-	4%	-	-
Restriction	1	-	1	2	3	2	4	6	1	1	1	-
	4%	-	4%	8%	12%	8%	16%	24%	4%	4%	4%	-
Normal	2	1	1	3	2	3	4	2	1	-	-	-
	8%	4%	4%	12%	8%	12%	16%	8%	4%	-	-	-
Total	3	1	2	5	7	5	10	12	2	2	1	-
	12%	4%	8%	20%	28%	20%	40%	48%	8%	8%	4%	-

Chi-	d	‘p’val
16.7	4	0.002

TREATMENT NAIVE:

3 patients were in the age group of 20 – 29 years , 1 (4%) had restrictive pattern and 2 (8%) had normal PFT.

2 patients were in the age group of 30 -39 years 1 (4%) had restrictive pattern and 1(4%) had normal PFT

7 patients were in the age group of 40-49 years . 2 (8%) had obstructive pattern and 3 (12%) had obstructive and 2 (8%) had normal PFT.

10 patients were in the age group of 50 to 59 years , 2 (8%) had obstructive pattern and 4 (16%) had restrictive and 4(16%) had normal PFT.

2 patients were in the age group of 60 – 69 years , 1 (4%) had obstructive pattern and 1 (4%) had restrictive

1 patients were in the age group of 70 – 79 years and had restrictive pattern

The incidence of PFT abnormality in the age group of 50 to 59 years was high when compared to other age group this was statistically significant.

On treatment group:

One patients was in the age group of 20-29 Years , Who had Normal PFT.

5 Patients were in the age group of 30-39 Years ,2 had restrictive and 3 had normal PFT.

5 Patients were in the age group of 40-49 Years ,2 had restrictive and 3 had normal PFT.

12 Patients were in the age group of 50-59 Years ,4 had obstructive, 6 had restrictive and 2 had normal PFT.

3 Patients were in the age group of 60-69 Years ,1 had obstructive, 1 had restrictive and 1 had normal PFT.

TABLE-9

SEVERITY OF PFT ABNORMALITY CORRELATED WITH SYMPTOM DURATION ON TREATMENT GROUP

	Total		
	3- 6 years	>6 yrs	
Mild	4	2	6
	16%	8%	24%
Moderate	2	1	3
	8%	4%	12%
Severe	1	1	2
	4%	4%	8%
Normal	2	1	3
	8%	4%	12%
Total	13	12	25
	52%	48%	100%

Chi-SquareValue	df	'p'value
0.422	2	0.81 NS

13 patients were on treatment for 3 – 6 years of them 7 patients had abnormal PFT4 (16%) patients had mild PFT abnormality , 2 (8%) had moderate PFT abnormality , 1 (4%) had severe PFT abnormality and 2 patients had normal PFT.

12 patients were on treatment for more than 6 years , of them 6 patients had abnormal PFT , 3 (12%) had mild PFT abnormality , 2 (8%) had moderate PFT abnormality , 1 (4%) severe PFT abnormality , 1 had normal PFT.

No statistical correlayion was found between the severity of PFT abnormality and duration of disease was found.

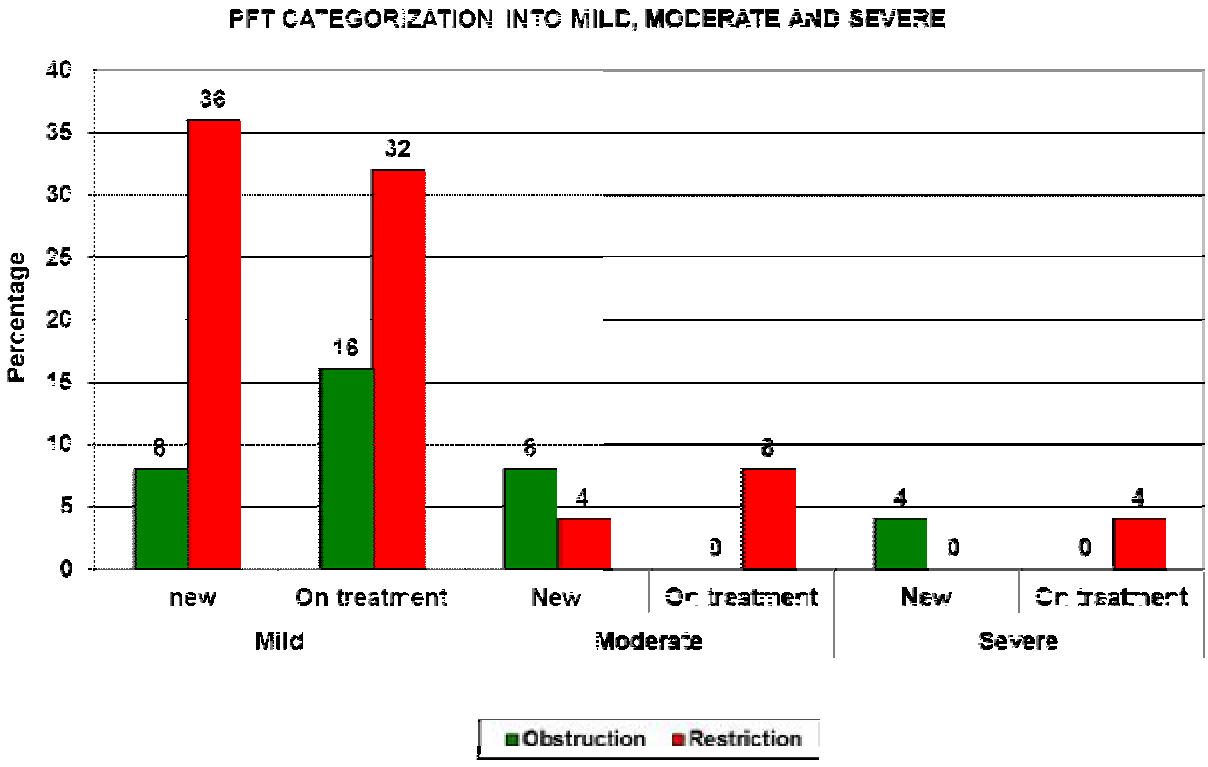


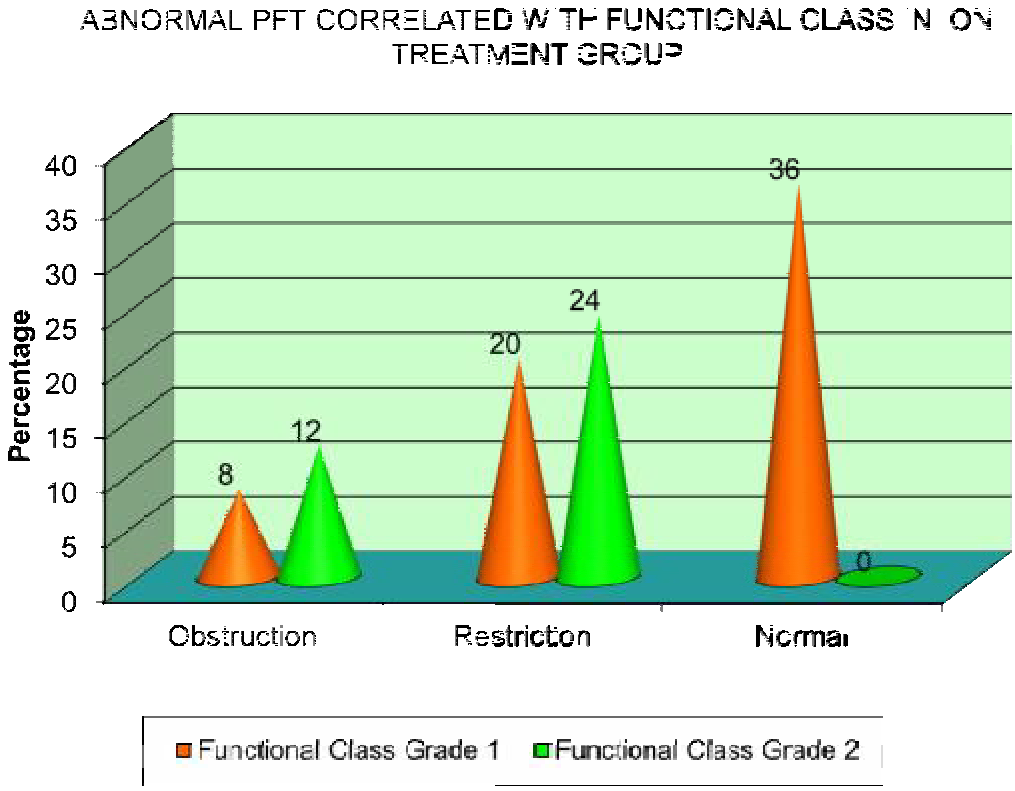
TABLE-10

ABNORMAL PFT CORRELATED WITH FUNCTIONAL CLASS IN ON TREATMENT GROUP

PFTFinding	FunctionalClass		Total
	Grade1	Grade2	
Obstruction	2	3	5
	8%	12%	20%
Restriction	5	6	11
	20%	24%	44%
Normal	9	0	9
	36%	0%	36%
Total	16	9	25
	64%	36%	100%

Chi- Square Value	df	'p' value
0.814	1	0.004

5 patients had obstructive PFT , among them 2 (8%) were in functional class I and 3 (12%) patients were in functional class II . 11 patients had restrictive PFT , 5 (20%) were in functional class I , 6 (24%) were in functional class II , 9 patients had normal PFT.



DISCUSSION

Rheumatoid arthritis (RA) is a chronic multi-system disease of unknown cause. It is a systemic inflammatory disease and affects 1-2% of the general population. A major portion of morbidity and mortality are due to RA are due to its extra-articular manifestations A variety of pulmonary manifestations are associated with RA[6] and lung disease is the second most common cause of death (18%) after infection (27%) inpatients with RA. Pleuro-pulmonary manifestations occur more commonly in men. Pulmonary function test abnormalities in RA can be restrictive (19-44%) if there is pleural or parenchymal involvement, or obstructive (16-38%) if there is obliterative bronchiolitis, bronchiectasis or cricoaryetenoid arthritis[23].

In our study the female to male ratio was 2:1. In a study conducted by Arnett FC et al, RA has a 3:1 predilection for women between the ages of twenty and fifty years[107].In a study conducted by RanigaS, Sharma Petal in 2006, the female to male ratiowas 3:1[108].The male to female ratio ranges from 1:2 to 1:4.

The average age of patients in our study was 46.5years.The mean age of onset of pulmonary disease was in the fifth or sixth decade. In a study conducted by Raniga etal, average age of male patients was 48.4 years and for females 45.8years[108].The mean duration of illness was 34.8 months. The mean age of onset of lung disease was in the fifth or sixth decade. The average age of patients in our study was comparable to that of other studies. However the mean duration of illness in our study was more than the other studies.

Rheumatoid factor results:

RA factor was positive in 70% of patients with RA in our study. RA factor was positive in twenty-five patients (83.3%). In the study by Raniga et al nearly 3/4th of patients with RA have rheumatoid factor positivity[109].

Respiratory symptoms and signs:

In our study patients with respiratory symptoms were 16%. Patients presented with cough, breathlessness, wheeze and combination of these. 7% had clinical evidence of respiratory involvement. In the study conducted by Raniga et al, six of the thirty patients had respiratory

complaints (20%)[108]. The symptoms included cough, breathlessness, wheeze, sputum production and chest pain. Only three patients(10%) had clinical evidence of respiratory involvement [presence of rhonchi and crackles]. In our study, more patients had respiratory signs than those who had respiratory symptoms.

PFT abnormalities in patients with rheumatoid arthritis:

Fifty patients underwent pulmonary function testing. 56% patients had abnormal PFTs 16% had obstructive and 40% had restrictive pattern in treatment naive and 64% patient had abnormal PFTs 20% had obstructive and 44% had restrictive pattern in on treatment group. Majority of patients in both restrictive and obstructive group had mild abnormality, lesser number of patients had moderate abnormality and very few patients had severe PFT abnormality. The incidence of obstructive PFT abnormality was more common in male patients in our study.

In patients with RA, bronchiectasis is more common in women (male to female ratio of 1:2.8). However, other causes of obstruction like obstructive bronchiolitis and follicular bronchiolitis are more common in men.

In our study patients with radiologically overt bronchiectasis were less. Hence there was a male preponderance with respect to obstructive defect.

The incidence of restrictive PFT abnormality was more common in female patients in our study. However, the incidence of ILD and pleural involvement that causes restriction is more common in men a study conducted by Gabbay et al[79]. In our study more female patients had restrictive PFT abnormality. This could be explained by the fact that only a small number of patients with RA were screened for lung involvement. Hence, they may not actually reflect the patients with ILD having restrictive PFT abnormality.

Majority of patients with PFT abnormality in our study were in the fifth and sixth decades. The difference between the age groups were not statistically significant.

In the study conducted by Raniga et al, spirometric evidence of lung involvement was present in eight patients (26.6%) [108]. Maximum abnormal PFTs were noted in the fifth and sixth decade. However the difference between the abnormalities in the age groups were not statistically significant.

In the study conducted by Fuld et al, the maximum abnormal PFTs were in the age group of 40-69 years with the peak incidence in the age group of 50-59. PFTs abnormalities were more in patients with respiratory symptoms when compared to those without them.

In the study conducted by Vitali.C et al, PFT abnormalities were seen more in patients with respiratory symptoms [110].

In our study, spirometric evidence of lung involvement was seen in 60%. 21(48.5%) patients out of 44 asymptomatic patients had an abnormal PFT.

In the study conducted in 2006 by Raniga N et al, spirometric evidence of lung involvement was present in eight patients [108]. Thus, spirometric abnormalities could be detected in asymptomatic patients also. HRCT was abnormal in eleven patients (36%) and hence more sensitive than spirometry to detect pleuropulmonary involvement in patients of RA. Spirometry picked up a larger number of abnormal PFTs in our study. Abnormalities were also seen in a significant number of a symptomatic patients.

Restrictive PFT abnormality

In our study, patients with reduced FVC was observed in 19 (37%) patients. Thirty nine patients (52%) had abnormal PFTs. 6 (15.4%) patients among the patients with abnormal PFTs had an abnormal chest radiograph. 3 (10.7%) patients with restrictive PFT abnormality had radiological evidence of reticular opacities. 3 (27.3%) patients with obstructive PFT had radiological evidence of hyperinflation. 2(6%) patients who had normal PFTs had an abnormal X-ray. Hence PFTs were more sensitive in detecting pulmonary abnormalities than chest radiographs. However when

both these investigations were used together, the yield of pulmonary abnormalities was better than either test alone.

In a study conducted by McDonagh et al, spirometric abnormalities were noted in 8/30 (26.6%) and radiological abnormality in 13% [62]. In a study conducted by Laitinen O et al, vital capacity (VC) and single-breath diffusing capacity for carbon monoxide of the lungs (DLco) were measured and chest X-ray evaluated in 129 patients with rheumatoid arthritis (RA)[83].Findings in the 123 cases were observed as follows: in one of the lung function tests or X-ray examinations, 35%; abnormal X-rays, 18%; reduced VC 28%; simultaneously low VC and Dco, 7%; and pathological findings in all three tests,2%. The patients with abnormal X-rays showed extremely low VC and Dco values. Changes in respiratory function involved restrictive impairment and diffusion defects, and the results further implied that restrictive changes develop early, where as decreased diffusing capacity is associated with more advanced rheumatoid lung. The disparity abnormal findings in chest X-ray changes and in lung function tests suggests that in examining pulmonary manifestations in patients with RA, both radiographic methods and pulmonary function tests should be used for relevant evaluation

The incidence of restrictive lung disease in our study was 37%. Most patients had mild restriction, lesser patients had moderate and least had severe restriction. Interstitial lung disease occurs in 19% of patients with RA irrespective of respiratory symptoms, however, early interstitial lung changes and subclinical alveolitis have been found in upto 40% of RA patients in a study conducted by Eisenberg H, McDonagh J et al[62]. Mean age at onset of ILD was the fifth or sixth decade. The HRCT study by Fewins et al of patients with RA revealed a high prevalence of ILD(44%) with maximum patients having mild restriction and lesser patients having moderate and severe restriction[112]. In the study conducted by Raniga et al, when all forms of HRCT diagnosed abnormalities are combined, there was a closer prevalence (37%) of ILD to the other studies. In a study conducted by McDonagh et al, HRCT findings consistent with ILD were seen in eleven out of thirty patients(36%), compare to the spirometric findings in 8/30(26.6%). The results of HRCT have not been shown to correlate with pulmonary function tests.

Obstructive PFT abnormality:

In our study, 9(18%) patients had evidence of obstruction on PFTs which was comparable to the reported prevalence of airway disease in RA. In a study conducted by Doyle et al in 2004, the pulmonary abnormalities

included two patients with hypoxia(12%), two with obstruction (12%), and three with restriction (18%) and four with AHR (23%)[105]. In a PFT survey of patients with rheumatoid arthritis, airway obstruction was observed in 9-37%, even in non-smoking patients. Perez T et al studied 50 patients with RA (ninemalesand41 females;meanage:57.8yr), which included 39 nonsmokers and 11 smokers(meancigaretteconsumption:15.3pack-yr) without radiographic evidence of RA-related lung changes. PFTs demonstrated airway obstruction (i.e., reduced FEV_1/VC) in nine patients (18%) compared to HRCT which picked up an abnormality in 70% of patients. In the study conducted by Fuld et al, after exclusion of smokers, the proportion of airway obstruction in patients with rheumatoid arthritis was 16%(versus0%incontrols), although the patients with rheumatoid arthritis still had more symptoms and respiratory disorders.

Correlation of PFT findings and duration of disease:

In our study the number of patients with restriction in treatment naive group is 40% and in on treatment group is 44%. However there was no correlation between severity of PFT abnormality and the duration of disease.

In a study conducted by Cervantes-Perez et al, no correlation was found between the disease duration, the number of patients and the severity of restrictive PFT abnormality. This could be explained by the fact that most of our patients had subclinical ILD when compared to the series of Cervantes-Perez et al[111].

In our study the number of obstructive PFTs also increased as the disease duration increased. However there was no correlation observed between the disease duration and severity of PFT abnormality

In a study conducted by Fuld et al, there was no relationship between the severity of obstructive abnormality, the duration of disease and type of treatment[106]. The data also suggest a strong association between pulmonary diseases in RA and cigarette smoking.

In the study conducted by Fuld et al, there was no relationship between airway obstruction, duration of rheumatoid arthritis and type of treatment. There was also no correlation between the severity of PFT abnormality and the duration of the disease.

In the study by Cervantes-Perez et al, there was no correlation between the number of patients with obstructive PFT abnormality and the duration of disease[111]

Correlation of severity of PFT abnormality and duration of disease:

In a study conducted by Cervantes-Perez et al, no correlation was found between the disease duration, the number of patients and the severity of restrictive PFT abnormality. This could be explained by the fact that most of our patients had subclinical ILD when compared to the series of Cervantes-Perez et al.

In our study ,9 (18%) patients had evidence of obstruction on PFTs which was comparable to the reported prevalence of airway disease in RA. In our study the number of obstructive PFTs increased as the disease duration increased, but it was not statistically significant. However there was no correlation observed between the disease duration and severity of PFT abnormality

In a study conducted by Fuld et al,there was no relationship between the severity of obstructive abnormality, the duration of disease and type of treatment. In a study conducted by Doyle et al in 2004, the pulmonary abnormalities included two patients with hypoxia (12%), two with obstruction (12%), and three with restriction (18%) andfour with AHR (23%). The data also suggest a strong association between pulmonary diseases in RA and cigarette smoking. In a PFT survey of patients with rheumatoid arthritis,airway obstruction was observed in 9-37%, even in non-smoking patients.

PerezT et al studied 50 patients with RA nine males and 41 females ; mean age: 57.8yr), which included 39 nonsmokers and 11smokers (mean cigarette consumption: 15.3pack-yr) without radiographic evidence of RA-related lung changes. PFTs demonstrated airway obstruction (i.e., reduced FEV_1/VC) in nine patients (18%) compared to HRCT which picked up an abnormality in 70%of patients..In the study conducted by Fuld et al, the maximum abnormal PFTs were in the age group of 40-69 years with the peak incidence in the age group of 50-59 years. After exclusion of smokers, the proportion of airway obstruction in patients with rheumatoid arthritis was 16% (versus 0% in controls), although the patients with rheumatoid arthritis still had more symptoms and respiratory disorders. There was no relationship between airway obstruction, duration of rheumatoid arthritis and type of treatment. There was also no correlation between the severity of PFT abnormality and the duration of the disease.

Correlation of PFT abnormality and functional class:.

The abnormal PFTs were found more commonly in functional class-2. This implied that patients who had a lung function abnormality on PFT had a more impaired functional class of RA. When the severity of PFT abnormality was

correlated with functional class of rheumatoid arthritis it was found that more patients with moderate obstruction were in functional class2 when compared to patients with mild obstruction. The severity of obstruction increased when the functional class of patients changed to class2 from class1. This implied that patients with more severe obstructive abnormality were functionally more limited when compared to those with a milder obstructive abnormality.

Correlation of DMARD and PFT abnormality:

No patient in our study had methotrexate induced acute pneumonitis. Life-threatening acute methotrexate pneumonitis occurs in 0.3-11.6% of rheumatoid arthritis patients treated with methotrexate, usually with in the first 6 months. A recent report by Khadadah et al [98] showing significant deterioration in lung function after 2years of treatment with methotrexate raised the issue of chronic toxicity, but Dawson et al found no such deterioration inlung function over 2 years with methotrexate. There was no correlation observed between the duration of DMARDs and PFT abnormality in our study. However a longitudinal study is warranted to assess the impact of long term methotrexate and chronic lung toxicity

Radiological abnormalities:

The incidence of radiological abnormality was 10.7%. with 37.5% of these patients showing reticulonodular opacities-The incidence of radiological abnormality ranges from 2-10% in patients with RA. Chest x-ray showed changes consistent with ILD in 9/150 (6%) patients with RA and X-ray chest was normal in 18/28 (64.2%) patients with HRCT positive ILD. In the study conducted by Raniga et al,abnormalities detectable on chest radiograph were 13.33%, chest x-ray showed changes consistent with ILD in 4/30 (13.3%) including bilateral reticular infiltrates in three and honeycombing in one and x-ray chest was normal in 7/11 (63.6%) patients with HRCT positive ILD.

In a study conducted by FrankSI and PerezT et al, evidence of interstitial fibrosis is seen at chest radiography in approximately 5% of patients with rheumatoid arthritis and at HRCT in 30%-40%. The chest radiograph may be normal in patients with early fibros is Most of these patients had respiratory symptoms.In a study conducted by VitaliH et al, the prevalence of ground glass opacities (GGOs) on HRCT in patients with

out respiratory symptoms was only 3% and none had honeycombing, in contrast to 26 and 23%, respectively in patients with respiratory symptoms.[15] .Chest radiograph is the least sensitive in detecting interstitial lung disease. In our study, the ability of PFTs to pick up an abnormality was better than the chest radiograph which were 52% and 10.7% respectively. However when both these investigations were combined, the sensitivity was better than either test alone.

In late stages, chest radiograph shows changes identical to that of Interstitial Pulmonary Fibrosis (IPF). Chest radiographs typically show a fine reticular or reticulonodular pattern involving the lower lung zones in early stages . With progression of disease, the reticular pattern becomes more coarse and diffuse, and honey combing may be seen. In our study the reticulonodular opacity consistent with ILD was seen in 3 (4%) of patients. This accounted for 37.5% of the abnormal chest radiographs.The radiological abnormality was in the form of reticulonodular opacity consistent with the diagnosis of ILD.

HRCT shows evidence of interstitial lung disease in eleven out of thirty patients and so the most sensitive of all parameters. It was evident that chest radiograph is the least sensitive in detecting interstitial lung disease.In our study, the ability of PFTs to pickup an abnormality was better than the chest radiograph which were 52% and 10.7% respectively.

CONCLUSIONS

- PFTs are a sensitive tool in picking up pulmonary involvement in rheumatoid arthritis.
- The incidence of abnormal PFTs was maximum in the age group of 41-60 years.
- PFT abnormalities were found in a more than half of patients with RA in our study.
- Restrictive lung disease was the commonest abnormality and was seenin 1/3 rd of patients
  - Obstructive airway disease was seen in 1/5 th of patients
- Most of the patients had mild degree of restrictive and obstructive abnormalities
- The number of abnormal PFTs increased as the disease duration increased.There was no correlation between the disease duration and the severity of PFT abnormality.
    - PFT abnormalities were encountered with greater frequency in patients of higher functional class of disability in rheumatoid arthritis.

There is increased incidence of PFT abnormality in on treatment group when compared to treatment naïve group this may be explained by the type of lung involvement (ex. If the patient had usual interstitial pneumonia the lung disease may progress or remain static) . but a longitudinal study is warranted.

SUMMARY

Lung involvement is one of the most important extra articular manifestations of rheumatoid arthritis. The incidence of restrictive lung disease observed in our study was 42%. A significant number of asymptomatic patients with RA had abnormal PFTs. The number of patients with PFT abnormalities increased as the duration of rheumatoid disease increased but the severity of these abnormalities did not increase. These PFT abnormalities were more commonly observed in patients with more impaired functional class. Pulmonary function tests are a sensitive measure in detecting early lung involvement in patients with rheumatoid arthritis. Pulmonary function testing when combined with chest radiography is cost effective and a good screening test for early detection of pleuro pulmonary involvement in patients with RA especially as HRCT and DLCO are not widely available and are expensive.

A key component of the evaluation is determination of the type of ILD, as all of the histopathologic types of idiopathic interstitial lung disease can occur in the context of RA . Often the cause and type of ILD can be determined by the combination of clinical presentation, PFTs, and HRCT. In a minority of cases, when these features are not typical for a given type of ILD and the patient is symptomatic, fit for surgery, and the biopsy would

change the therapeutic approach , characterization of the ILD by lung biopsy is often appropriate

An early effort to diagnose the pattern of lung involvement is required for specific management. The prognosis of RA-ILD depends on the histopathologic subtype . For many patients with RA-ILD, the pulmonary abnormalities do not progress and may remain subclinical

The improvement of pulmonary function depends upon the specific histopathology of lung involvement .Hence early diagnosis and appropriate therapy is needed for better quality of life in these patients.

BIBLIOGRAPHY

1. Kasper DL, Braunwald.E et al.“Rheumatoid Arthritis”. Harrisons Principles of Internal Medicine.2005;Vol 2:1968.

2. Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, Matteson EL. “Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years”. Arthritis Rheum 2003;48:54–58.

3. Turesson C, Matteson EL. “Management of extra-articular disease manifestations in rheumatoid arthritis”.Curr Opin Rheumatol 2004;16:206–211.

4. Firestein GS, “Etiology and pathogenesis of rheumatoid arthritis”. Kelly's Textbook of Rheumatology; Ruddy S, Harris E, Sledge C; 6th ed., W. B. Saunders, Philadelphia.

5. Linos A, Worthington JW, O'Fallon WM, Kurland LT. “The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence, and mortality”. Am J Epidemiol. 1980; 111:87-98.

6. Boers M, Dijkmans B, Gabriel S, Maradit-Kremers H, O'Dell J, Pincus T. (2004) “Making an impact on mortality in rheumatoid arthritis”. Arthritis Rheum 50:1734–9.

7. Horler AR, Thompson M: “The pleural and pulmonary complications of rheumatoid arthritis”. Ann Intern Med 1959; 50:1179-1203.

8. Anaya JM, Diethelm L, Ortiz LA, et al.: “Pulmonary involvement in rheumatoid arthritis”. Semin Arthritis Rheum 1995; 24:242-254.

9. Sahn SA. “The pathophysiology of pleural effusions”. Annu Rev Med 1990;41:7-13.

10. Lillington GA, Carr DT, Mayne JG: “Rheumatoid pleurisy with effusion”. Arch Intern Med 1971;128:764-768.

11. Joseph J, Sahn SA: “Connective tissue diseases and the pleura”. Chest 1993; 104:262-270.

12. Dawson JK, Fewins HE, Desmond J, et al. “Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests”. Thorax 2001; 56:622-627.

13. Chou CW, Chang SC: “Pleuritis as a presenting manifestation of rheumatoid arthritis: diagnostic clues in pleural fluid cytology”. Am J Med Sci 2002;323:158-161.

14. Flatley F: “Rheumatoid pulmonary disease”. N Engl J Med 1959; 261:1105-1108.

15. Portner MM,Gracie WA. “Rheumatoid lung disease with cavitary nodules,pneumothorax and eosinophilia”.N Engl J Med 1966;275:697

16. Dawson JK, Graham DR, Desmond J, Fewins HE, Lynch MP. “Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT

scanning and pulmonary function tests". Rheumatology (Oxford) 2002;41:262–267.

17. Gilligan DM, Pugnere N, Antonini MT, Arnaud M, Melloni B, Treves R, Bonnaud F. "Airway obstruction and rheumatoid arthritis". Eur Respir J 1997;10:1072–1078.

18. Geddes DM, Webley M, Emerson PA."Airways obstruction in rheumatoid arthritis". Ann Rheum Dis 1979;38:222–225.

19. Perez T, Remy-Jardin M, Cortet B. "Airways involvement in rheumatoid arthritis: clinical, functional and HRCT findings". Am J Respir Crit Care Med 1998;157:1658–1665.

20. Remy-Jardin M, Remy J, Cortet B, Mauri F, Delcambre B. "Lung changes in rheumatoid arthritis: CT findings". Radiology 1994;193:375–382.

21. Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M. "Bronchiolar disease in rheumatoid arthritis". Am J Respir Crit Care Med 1996;154:1531–1536.

22. Shadick NA., Fanta CH, Weinblatt ME, O'Donnell W, Coblyn JS. "Bronchiectasis: a late feature of severe rheumatoid arthritis". Medicine 1994;73:161–170.

23. Helmers R, Galvin J, Hunninghake GW. "Pulmonary manifestations associated with rheumatoid arthritis". Chest 1991;100:235–239.

24. M. J. Plant, M. M. O'Sullivan, P. A. Lewis, J. P. Camilleri, E. C. Coles, and J. D. Jessop. "What factors influence functional ability in patients with rheumatoid arthritis. Do they alter over time?" Rheumatology, September 1, 2005; 44(9): 1181 - 1185.

25. Gibson B, Howard H, et.at. “Radiographic progression in rheumatoid arthritis: Does it reflect outcome?” Does it reflect treatment? Ann Rheum Dis, November 1, 2001; 60(90003):47-50.

26. Fleming.A,June.M,Corbett.M. “Incidence of joint involvement in early RA.Rheumatology”. 1976;15(2):92-96.

27. Turesson C, Jacobsson LT. “Epidemiology of extra-articular manifestations in rheumatoid arthritis”. Scand J Rheumatol 2004;33:65–72.

28. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. “Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years”. Ann Rheum Dis 2003;62:722–727.

29. Lindqvist E and Eberhardt K. “Mortality in rheumatoid arthritis patients with disease in the 1980”. Ann Rheum Dis 1999;58:114.http://rheumatology.oxfordjournals.org/cgi/ijlink?linkType=FULL&journal Code=annrheumdis&resid=58/1/1

30. Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman A, Symmons DPM. “Mortality in early inflammatory polyarthritis”. Arthritis Rheum 2002;46:2010–9.

31. Boers M, Dijkmans B, Gabriel S, Maradit-Kremers H, O'Dell J, Pincus T. “Making an impact on mortality in rheumatoid arthritis”. Arthritis Rheum 2004; 50:1734–9.

32. Horler AR, Thompson M: “The pleural and pulmonary complications of rheumatoid arthritis”. Ann Intern Med 1959;50:1179-1203.

33. Anaya JM, Diethelm L, Ortiz LA, et al.: “Pulmonary involvement in rheumatoid arthritis”. Semin Arthritis Rheum 1995;24:242-254.

34. Lillington GA, Carr DT, Mayne JG: “Rheumatoid pleurisy with effusion”. Arch Intern Med 1971;128:764-768.

35. Joseph J, Sahn SA: “Connective tissue diseases and the pleura”. Chest 1993;104:262-270.

36. Walker WG, Wright V. “Rheumatoid pleuritis”.Ann Rheum Dis 1967;26:467

37. Sahn SA: “The pathophysiology of pleural effusions”. Annu Rev Med 1990;41:7-13.

38. Stanek KA, Mills KA: “Pleural effusion with rheumatoid arthritis”. S D J Med 1991;44:61-63.

39. Sahn SA, Kaplan RL, Maulitz RM, Good JT Jr: “Rheumatoid pleurisy. Observations on the development of low pleural fluid pH and glucose level”. Arch Intern Med 1980;140:1237-1238

40. Carr DT,Mayne JG. “Pleurisy with effusion in rheumatoid arthritis, with reference to low concentration of glucose in pleural fluid”.Am Rev Respir Dis 1962;85:345

41. Boddington MM,Spriggs AI,Morton JA,Mowatt AG. “Cytodiagnosis of rheumatoid pleural effusions”. J Clin Pathol 1971;24:95.

42. Dawson JK, Fewins HE, Desmond J, et al. “Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis”. Ann Rheum Dis 2002; 61:517-521.

43. Chou CW, Chang SC: “Pleuritis as a presenting manifestation of rheumatoid arthritis: diagnostic clues in pleural fluid cytology”. Am J Med Sci 2002;323:158-161.

44. Flatley F: “Rheumatoid pulmonary disease”. N Engl J Med 1959; 261:1105- 1108.

45. Portner MM,Gracie WA. “Rheumatoid lung disease with cavitary nodules,pneumothorax and eosinophilia”. N Engl J Med 1966;275:697.

46. Helmers R, Galvin J, Hunninghake GW.“Pulmonary manifestations associated with rheumatoid arthritis”. Chest 1991;100:235–239.

47. Panettiere F,Chandler BF,Libcke JH. “Pulmonary cavitation in rheumatoid disease”. Am Rev Respir Dis 1968;97:89.

48. Eraut D,Evans J,Caplin M. “Pulmonary necrobiotic nodules with and without rheumatoid arthritis”.Br J Dis Chest 1978;72:301.

49. Walters MN, Ojeda VJ. “Pleuropulmonary necrobiotic rheumatoid nodules. A review and clinicopathological study of six patients”. Med J Aust 1986; 144:648–651.

50. Ziff M. “The rheumatoid nodule”. Arthritis Rheum 1990;33:761–767.

51. Caplan A. “Certain unusual radiographic appearances in the chest of coal- miners suffering from rheumatoid arthritis”. Thorax 1953;8:19–37.
http://pats.atsjournals.org/cgi/external_ref?access_num=13029155&link_type=MED

52. Scadding JG. “The lungs in rheumatoid arthritis”. Proc R Soc Med 1969;62:227

53. Patterson CD,Harville WE,Pierce JA. “Rheumatoid lung disease”. Ann Intern Med 1965;62:685

54. Hyland RH,Gordon DA,Broder I,et al: “A systematic controlled study of pulmonary abnormalities in rheumatoid arthritis”: J Rheumatol 1983; 10:395-405.

55. Jurik AG,Davidsen D,Graudal H: “Prevalence of pulmonary involvement in rheumatoid arthritis and its relationship to some characteristics of patients: A radiological and clinical study”. Scand J Rheumatol 1982;11:217-224.

56. Shannon TM,Gale ME: “Non cardiac manifestations of RA in the thorax”. J Thorac Imaging 1992;7:19-29.

57. Vessey MP, Villard-Mackintosh L, Yeates D. “Oral contraceptives, cigarette smoking and other factors in relation to arthritis”. Contraception 1987;35:457–464.

58. Albano SA, Santana-Sahagun E, Weisman MH. “Cigarette smoking and rheumatoid arthritis”. Semin Arthritis Rheum 2001;31:146–159.

59. Harrison BJ. “Influence of cigarette smoking on disease outcome in rheumatoid arthritis”. Curr Opin Rheumatol 2002;14:246–252.

60. Saag KG, Kolluri S, Koehnke RK, Georgou TA, Rachow JW, Hunninghake GW, Schwartz DA. “Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities”. Arthritis Rheum 1996;39:1711–1719.

61. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, Ronnelid J, Harris HE, Ulfgren AK, Rantapaa-Dahlqvist S, et al. “A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination”. Arthritis Rheum 2006;54:38–46.

62. McDonagh J, Greaves M, Wright AR, Heycock C, Owen JP, Kelly C. “High resolution computed tomography of the lungs in patients with rheumatoid arthritis and interstitial lung disease”. Br J Rheumatol 1994;33:118–122.
http://pats.atsjournals.org/cgi/ijlink?linkType=ABST&journalCode=rheu

matology&resid=33/2/118

63. Biederer J, Schnabel A, Muhle C, Gross WL, Heller M, Reuter M.“Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis”. Eur Radiol 2004;14:272–280.

64. Ayhan-Ardic FF, Oken O, Yorgancioglu ZR, Ustun N, Gokharman FD. "Pulmonary involvement in lifelong non-smoking patients with rheumatoidarthritis and ankylosing spondylitis without respiratory symptoms". Clin Rheumatol 2006;25:213–218.

65. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, Heimisdottir M, Sigurdardottir SL, Valdimarsson H, Vikingsson A. "The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis". Rheumatology (Oxford) 2006;45:734–740.

66. Popper MS,Bogdonoff ML,Hughes RL. "Interstitial rheumatoid lung disease:a reassessment and review of literature".Chest 1972;62:243.

67. Flatley F: "Rheumatoid pulmonary disease". N Engl J Med 1959;261:1105-1108

68. Yousem SA,Colby TV,Carrington CB: "Lung biopsy in RA".Am Rev Respir Med 1985;131:770-777.

69. Yoshinouchi T,Ohtsuki Y,Fujita J,et al: "Non specific interstitial pneumonia pattern as pulmonary involvement of rheumatoid arthritis". Rheumatol Int 2005,in press

70. Martinez F, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, Flaherty KR, Schwartz DA, Noble PW, Raghu G, et al. "The clinical course of patients with idiopathic pulmonary fibrosis". Ann Intern Med 2005;142:963–967.

71. Hakala M. “Poor prognosis in patients with rheumatoid arthritis hospitalized for interstitial lung fibrosis”. Chest 1988;93:114–118.

72. Lamblin C, Bergoin C, Saelens T and Wallaert B. “Interstitial lung diseases in collagen vascular diseases”. Eur Respir J 2001; 18:69S-80S.

73. Zerhouni EA, Naidich DP, Stitik FP, Khouri NF, Siegelman SS. “Computed tomography of the pulmonary parenchyma. Part 2: Interstitial disease”. J Comput Assist Tomogr 1985; 1:54-64.

74. Akira M, Sakatani M, Hara H. “Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses”. J Comput Assist Tomogr 1999; 23:941-948.

75. Biederer J, Schnabel A, Muhle C, et al. “Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis”.Eur Radiol 2004;14:272-280.

76. Horton MR. “Rheumatoid arthritis associated interstitial lung disease”. Crit Rev Comput Tomogr 2004;45:429-440.

77. Banks J, Banks C, Cheong B, et al. “An epidemiological and clinical investigation of pulmonary function and respiratory symptoms in patients with rheumatoid arthritis”. Q J Med 1992; 85:795-806.

78. Jurik AG, Davidsen D, Graudal H. “Prevalence of pulmonary involvement in rheumatoid arthritis and its relationship to some characteristics of the patients: a radiological and clinical study”. Scand J Rheumatol 1982; 11:217-224.

79. Gabbay E, Tarala R, Will R, et al. “Interstitial lung disease in recent-onset rheumatoid arthritis”. Am J Respir Crit Care Med 1997; 156:528-535.

80. Wadsworth SJ and Hansell DM. “High resolution computed tomography (HRCT) of the lung in rheumatoid arthritis”. Imaging 1999; 11:53-59.

81. Garcia.JG, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Copper NS et al. “The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis”. Arthritis Rheum 1988; 31:315-24.

82. Tanaka N., Kim JS, Newell JD, Brown K., Cool CD, Meehan R, Emoto T, Matsumoto T, and Lynch DA. “Rheumatoid Arthritis-related Lung Diseases: CT Findings”. Radiology 2004;232:81-91.

83. Laitinen O, Nissilä M, Salorinne Y, Aalto P. “Pulmonary involvement in patients with rheumatoid arthritis”. Scand J Respir Dis. 1975;56(6):297-304.

84. Hassan WU, Keaney NP, Holland CD, Kelly CA. “High resolution computed tomography of the lung in lifelong nonsmoking patients with rheumatoid arthritis”. Ann Rheum Dis 1995; 54:308-310.

85. Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, Lake FR. "Interstitial lung disease in recent onset rheumatoid arthritis". Am J Respir Crit Care Med 1997; 156: 528 – 535. http://pats.atsjournals.org/cgi/ijlink? linkType=ABST&journalCode=ajrccm&resid=156/2/528

86. Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M. "Bronchiolar disease in rheumatoid arthritis". Am J Respir Crit Care Med 1996;154:1531–1536.

87. Geddes DM, Webley M, Emerson PA. "Airways obstruction in rheumatoid arthritis". Ann Rheum Dis 1979;38:222–225. http://pats.atsjournals.org/cgi/ijlink?linkType=ABST&journalCode=annrheumdis&resid=38/3/222

88. Radoux V, Menard HA, Begin R, Decary F, Koopman WJ. "Airways disease in rheumatoid arthritis patients". Arthritis Rheum 1987;30:249–256. http://pats.atsjournals.org/cgi/external_ref?access_num=3566819&link_type=MED

89. Homma S, Kawabata M, Kishi K, Tsuboi E, Narui K, Nakatani T, Uekusa T, Saiki S, Nakata K. "Diffuse panbronchiolitis in rheumatoid arthritis". Eur Respir J 1998;12:444–452.

90. Vergnenegre A, Pugnere N, Antonini MT, Arnaud M, Melloni B, Treves R, Bonnaud F. “Airway obstruction and rheumatoid arthritis”. Eur Respir J 1997;10:1072–1078.

91. duBois RM,Geddes DM: “Obliterative bronchiolitis,cryptogenic organizing pneumonia,bronchiolitis obliterans organizing pneumonia: Three names for two different conditions”. Eur Respir J 1991;4:774-775.

92. Murphy KC,Atkins CJ,Offer RC et al. “Obliterative bronchiolitis in two rheumatoid arthritis patients treated with pencillamine”. Arthritis Rheum 1981;24:557.

93. Howling SJ,Hansell DM,Wells AV,et al: “Follicular bronchiolitis:Thin section CT and histologic findings”. Radiology 1999;212:637-642.

94. hadick NA., Fanta CH, Weinblatt ME, O'Donnell W, Coblyn JS. “Bronchiectasis: a late feature of severe rheumatoid arthritis”. Medicine 1994;73:161–170.

95. Gardner DL,Duthie JJR,Mcleod J,Allan WSA. “Pulmonary hypertension in rheumatoid arthritis".Scott Med J 1957;ii:183.

96. Tribe CR. “Amyloidosis in rheumatoid arthritis”.Mod Trends Rheumatol 1966;1:121.

97. Lateef O, Shakoor N, Balk RA. “Methotrexate pulmonary toxicity”. Expert Opin Drug Saf 2005;4:723–730.

98. Khadadah ME, Jayakrishnan B, Al-Gorair S, Al-Mutairi M, Al-Maradni N, Onadeko B, Malaviya AN. “Effect of methotrexate on pulmonary function inpatients with rheumatoid arthritis–a prospective study”. Rheumatol Int 2002;22:204–207.

99. Beyeler C, Jordi B, Gerber NJ, Im Hof V. “Pulmonary function in rheumatoid arthritis treated with low-dose methotrexate: a longitudinal study”. Br J Rheumatol 1996;35:446–452.100,101.Cooper JA Jr, White DA, Matthay RA: “Drug-induced pulmonary disease. Part 2: Noncytotoxic drugs”. Am Rev Respir Dis 1986;133:488-505.

102. Cortet B ,Remy-Jardin M , Mauri F, Delcambre B. “Lung changes in rheumatoid arthritis: CT findings”. Radiology 1994;193:375–382.

103. Terasaki.H, Fujimoto.K, et. al. “Respiratory symptoms in rheumatoid arthritis: Relation between HRCT findings and functional impairment”. Radiation Medicine 2004;22:179-85.

104. Perez T, Remy-Jardin M, Cortet B. “Airways involvement in rheumatoid arthritis: clinical, functional and HRCT findings”. Am J Respir Crit Care Med 1998;157:1658–1665.

105. Doyle.P,Borman.P et al. “HRCT of the lungs in patients with RA” 1999;19:19-22.

106. Fuld JP, Johnson MK, Cotton MM, et al. “A longitudinal study of lung function in nonsmoking patients with rheumatoid arthritis”. Chest 2003;124:1224-1231.

107. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Copper NS et al. “The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis”. Arthritis Rheum 1988; 31:315-24.

108. Raniga S, Sharma P, Kaur G, Arora A, Khalasi Y, Vohra PV. “Interstitial Lung disease in Rheumatoid arthritis "- a study of thirty cases.2006;16(4):835-39.

109. Freyha R,Ayyash R. “Rheumatoid disease without arthritis”. John Hopkins Medical Journal.1976:1399 (4) 69-72.

110. Vitali.C et. al. “Lung function abnormalities in different connective tissue disorders”. 1986.5;(2):181-8.

111. Cervantes-Perez C, Toro-Perez AH,Rodriguez-Jurado-P: “Pulmonary involve- ment in rheumatoid arthritis”.JAMA 243:1715-1719,1980.

112. Fewins HE,McGowan I et al. “HRCT in rheumatoid arthritis associated pulmonary disease”. Br J Rheumatol.1991;30(3)214-6.

ANNEXURE - I

THE 2010 ACR-EULAR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

	Score
Target population (Who should be tested?): Patients who 1. have at least 1 joint with definite clinical synovitis (swelling) ***** 2. with the synovitis not better explained by another disease **â€**	
Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥6/10 is needed for classification of a patient as having definite RA)**â€¡**	
A. Joint involvement **Â§**	
1 large joint**Â¶**	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints) **#**	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint) ******	5
B. Serology (at least 1 test result is needed for classification) **â€ â€**	

	Score
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms**Â§Â§**	
<6 weeks	0
≥6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

â€ Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

â€¡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

Â§ Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved

joints, with placement into the highest category possible based on the pattern of joint involvement.

Â¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

â€ â€ Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

â€¡â€¡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

Â§Â§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness)

of joints that are clinically involved at the time of assessment, regardless of treatment status.

ANNEXURE - II

PROFORMA

DATE:

HOSPITAL OP/IP NO:

1. NAME :

2. AGE :

3. SEX :

4. OCCUPATIONAL HISTORY :

5. HISTORY OF EXPOSURE TO POLLUTANTS: YES -/ NO-

6. PRESENTING COMPLAINTS –

a. RELATED TO MUSCULOSKELETAL SYSTEM –

1.PAIN-

2.SWELLING-

3.RESTRICTION-

4.DEFORMITY-

b. RELATED TO RESPIRATORY SYSTEM-

i. COUGH - iv

.EXPECTORATION- ii. BREATHLESNESS –

v CHEST PAIN-

iii. WHEEZE - vi HEMOPTYSIS-

7. HISTORY OF BRONCHIAL ASTHMA. YES -/NO-

8. HISTORY OF SMOKING : YES /NO- IF YES -

TYPE OF TOBACCO-

NUMBER OF BEEDIS/CIGARRETES- NUMBER OF YEARS SMOKED- SMOKING INDEX-

(SMOKERS ARE EXCLUDED)

9. HISTORY OF COPD : YES-/NO-

10. HISTORY OF PULMONARY TUBERCULOSIS- YES -/NO-

11. TIME SINCE R A DIAGNOSIS-

12. TIME SINCE ON MEDICATIONS-

13. TREATMENT DETAILS-

14. ON EXAMINATION –

a. GPE-

PALLOR:YES-/ NO-

ICTERUS: YES-

/NO- CYANOSIS:

YES-/NO-

CLUBBING:YES-

/NO-

LYMPHADENOPATHY:YES-

/NO- PEDAL EDEMA:YES-/NO-

b. SYSTEMIC EXAMINATION

RESPIRATORY SYSTEM-

CARDIOVASCULAR SYSTEM-

CENTRAL NERVOUS SYSTEM

- PER ABDOMEN-

MUSCULOSKELETAL
- SYSTEM

	MCP	PIP	WR	EL	SH	MTP	PIP	AN	KN	HIP AA
SWELLING-										
RESTRICTIO N-										
DEFORMITY-										

SPO

2: INVESTIGATIONS:

ROUTINE:

CX

R: PFT

IMPRESSION:

ANNEXURE- III

FUNCTIONAL CLASS OF RHEUMATOID ARTHRITIS

GRADE-1 -NO HANDICAP. CAN CARRY ON ALL DAILY ACTIVITIES

GRADE-2 -MODERATE RESTRICTION OF ACTIVITIES BUT

INDEPENDENT

GRADE-3 -MARKED RESTRICTION OF ACTIVITIES MOSTLY LIMITED

TO SELF CARE.NEEDS ASSISTANCE

GRADE-4 -BED OR CHAIR BOUND. INCAPACITATED AND DEPENDENT

LIST OF ABBREVIATIONS USED

PFT	-	Pulmonary function test
RA	-	Rheumatoid Arthritis
ILD	-	Interstitial lung disease
BOOP	-	Bronchiolitis obliterans organizing pneumonia
OB	-	Obliterative bronchiolitis
CB	-	Constrictive bronchiolitis
FB	-	Follicular bronchiolitis
NSIP	-	Non specific interstitial pneumonitis
UIP	-	Usual interstitial pneumonitis
DMARDs	-	Disease modifying antirheumatoid drugs
MTX	-	Methotrexate
HRCT	–	High Resolution computed Tomography.
CXR	–	Chest Radiogram
FEV_1	–	Forced Expiratory Volume in First Second
FVC	–	Forced Vital Capacity
FEF 25-75/MMFR	–	Maximum Mid Expiratory Flow Rate
PEFR	–	Peak Expiratory Flow Rate.

MASTER CHART

S.No	name	age	sex	pain	swelling	restriction	deformity	resp sym	time-diag	on medi	methotrex	swelling	restriction	deformity	spo2	CXR	PFT	F.C	RS	FEV1	% PRE	FVC	%PRE	FEV1/VC	PEF	% PRE	MMEF	%PRE
1	LATHAMANLR	40	F	3 Y	PRES	NO	NO	NO	3 Y	3Y	4/ WEEK	PRES	NO	NO	N	NAD	Mild Restrictior	1	NVBS	1.55	63	2.02	70	77	4.04	71	1.25	42
2	PUSHPA R	38	F	3 MON	PRES	NO	NO	NO	3 MON	3 MON	3/WEEK	PRES	NO	NO	N	NAD	Normal	1	NVBS	1.91	81	2.12	78	90	3.43	105	3.13	110
3	SHANTHAMMA	52	F	10 MON	PRES	MC PP A	NO	NO	1.5 MON	1.5 MON	3/WEEK	PRES	MC PP A	NO	N	Alveolar Opacity	Mild Restrictior	1	CR+	2.04	79	2.23	71	91	3.88	65	2.52	88
4	MERCY M A	63	F	3 Y	PRES	MC MT	NO	NO	3 Y	1.5ON	3/WEEK	PRES	MC MT	NO	N	NAD	Normal	1	NVBS	1.91	91	2.34	90	82	2.94	93	2.04	90
5	RANGAMMA	45	F	3 Y	PRES	YES	NO	NO	2 Y	3 MON	2/WEEK	PRES	MC MT	MTP	N	NAD	Normal	1	NVBS	2.04	76	2.53	79	81	5.5	91	1.88	62
6	VENKATESH M	43	M	2 Y	PRES	MC PP W	PP	COU-5 D	1.5 Y	1 Y	2/WEEK	PRES	MC PP W	PP	N	NAD	oderate Obstruct	1	NVBS	1.52	51	2.02	57	75	1.97	42	1.21	37
7	VIJAYALAKSHMI	46	F	10 MON	NO	NO	NO	NO	10 MON	8 MON	3/WEEK	PRES	NO	NO	N	NAD	Normal	1	NVBS	2.21	87	2.37	78	93	4.83	138	2.83	98
8	NIRMALA M	46	F	3 Y	PRES	PIP	PIP-4	NO	1 Y	10 MON	3/WEEK	PRES	PIP	PIP	N	NAD	Mild Restrictior	1	NVBS	1.7	61	2.05	62	83	7.68	124	1.64	53
9	NAGARATHNA M	54	F	7 MON	NO	NO	NO	CO-4 D	7 MON	2 MON	3/WEEK	PRES	NO	NO	N	NAD	oderate Restrict	1	CR+ WH+	1.09	50	1.3	50	84	3.04	57	1.06	43
10	GNANASOUNDARI	57	F	2Y	NO	NO	NO	NO	5 Y	5 Y	3/WEEK	PRES	NO	NO	N	NAD	Normal	1	NVBS	1.87	78	2.26	77	83	5.42	95	2.01	76
11	SITALAKSHMI	55	F	3 Y	PRES	NO	NO	NO	3 Y	3 Y	3/WEEK	PRES	NO	NO	N	NAD	Mild Restrictior	1	NVBS	1.49	69	1.65	64	90	6.14	116	1.97	81
12	R RAMESH	52	M	3 MON	PRES	NO	NO	NO	3 MON	1.5 MON	2/WEEK	PRES	NO	NO	N	NAD	oderate Obstruct	1	NVBS	3.27	86	4.37	93	75	4.94	92	2.51	64
13	FAMIDA	44	F	5 Y	PRES	NO	NO	NO	5 Y	1 MON	3/WEEK	PRES	NO	NO	N	NAD	Normal	1	NVBS	2.09	80	2.49	81	84	3.92	110	2.59	87
14	JAYAMMA	50	F	3 Y	PRES	MC PP MT	MT,MC	NO	3 MON	1 DAY	NO	PRES	MC PP MT	MC MT	N	NAD	Normal	2	CR+	1.42	61	1.66	60	86	3.44	104	1.79	67
15	AMARNATH	28	M	6 MON	PRES	NO	NO	NO	1 MON	1 MON	2/WEEK	PRES	NO	NO	N	NAD	Mild Restrictior	1	NVBS	3.18	80	3.91	82	81	4.13	76	2.92	67
16	KATYAYANI	52	F	1 Y	PRES	K WR MC	NO	NO	1 Y	1 Y	3/WEEK	PRES	K WR MC	NO	N	NAD	Normal	1	NVBS	1.78	65	2.32	70	77	2.95	80	1.46	49
17	MUTHAMMA	70	F	2 Y	PRES	MC MT W	MC MT	NO	1 Y	8 MON	3/W BEF	PRES	MC MT W	MC	N	NAD	Normal	2	CR+	0.46	38	0.5	33	92	1.22	29	0.64	44.1
18	MAMATHA	32	F	3 Y	PRES	NO	NO	NO	3 Y	1 Y	2/WEEK	PRES	NO	NO	N	NAD	Mild Restrictior	1	NVBS	2.37	86	2.82	88	84	4.02	65	2.54	77
19	YASHODAMMA	49	F	1 Y	PRES	MC MT K	NO	NO	1 Y	1 Y	3/WEEK	PRES	MC MT K	NO	N	NAD	Mild Restrictior	1	NVBS	1.64	73	1.98	75	83	4.58	85	1.68	65
20	SATHISH	62	M	1 Y	PRES	NO	NO	COU-4D	1 Y	8 MON	NO	PRES	NO	NO	N	NAD	Mild Restrictior	1	CR+	1.85	70	2.39	72	77	6.36	86	1.56	57
21	SUMITRA K	53	F	1 Y	PRES	MC A MT	MC	NO	8 MON	8 MON	1/WEEK	PRES	MC A MT	MC	N	NAD	Mild Restrictior	1	NVBS	1.38	64	1.58	61	87	3.5	66	1.68	68
22	VIDHYA	27	F	2 Y	PRES	MC PP	NO	NO	2 Y	2 Y	2/WEEK	PRES	MC PP	NO	N	NAD	Normal	1	NVBS	2.84	97	3.14	93	90	6.63	104	3.42	97
23	SHEELA	53	F	1.5 Y	PRES	NO	NO	NO	1 Y	1 Y	NO	PRES	NO	NO	N	NAD	Normal	1	NVBS	2.26	93	2.91	99	78	356	104	1.9	70
24	SHOBHA	55	F	6 MON	PRES	MC W E	NO	NO	4 MON	4 MON	4/WEEK	PRES	NO	NO	N	NAD	Mild Obstructior	1	NVBS	1.73	84	1.85	75	94	411	133	3.09	132
25	SMITHA	25	F	8 MON	PRES	K A	NO	NO	7 MON	7 MON	3/WEEK	PRES	K A		N	NAD	Normal	1	NVBS	2.48	82	2.89	83	86	344	88	3.09	85

BR=Breathlessness	MC P=Knuckle
CO=Cold	PP/PIP=Proximal interphalange
Cou=Cough	EL/E=Elbow
WH=wheezing	WR/W=Wrist
ALL=Allergy	A/An=Ankle
	K/Kn=Knee
	MT/MTP=Metotarsophalangeal

S.No	name	age	sex	pain	swelling	restriction	deformity	resp sym	time-diag	on medi	methotrex	swelling	restriction	deformity	spo2	CXR	PFT	F.C	RS	FEV1	% PRE	FVC	%PRE	FEV1/VC	PEF	% PRE	MMEF	%PRE
1	ANURADHA	46	F	4 Y	PRES	YES	NO	NO	4 Y	4 Y	2/WEEK	PRES	MC	NO	N	NAD	Normal	1	NVBS	2.36	97	2.58	93	91	5.16	92	3.45	116
2	DEVAKI. R	32	F	12 Y	PRES	PRES	PRES	NO	5 Y	3 Y	3/WEEK	PRES	MC PIP	MC MT	N	NAD	Mild Restriction	2	NVBS	1.87	72	2.08	70	90	4.4	75	2.85	91
3	M SUSHEELAMMA	55	F	12 Y	PRES	YES	NO	NO	12 Y	3Y	2/WEEK	PRES	MC MT	NO	N	NAD	Normal	1	CR+	1.62	80	1.85	77	88	2.21	73	1.74	75
4	M P KAMALA	48	F	4 Y	PRES	NO	NO	NO	4 Y	5Y	NO	PRES	EL	NO	N	NAD	Normal	1	NVBS	2.48	94	3.03	95	82	4.36	121	2.6	88
5	MURAHARI	50	M	3 Y	PRES	NO	NO	NO	4 Y	3 Y	3/WEEK	PRES	NO	NO	N	NAD	Mild Restriction	1	NVBS	1.82	73	2.19	73	83	3.38	82	1.99	72
6	HEERA BAI	44	F	10 Y	PRES	NO	NO	NO	5 Y	5 Y	3/WEEK	PRES	MCP	NO	N	NAD	Mild Restriction	2	CR+	2.09	72	2.51	72	83	6.14	96	2.23	68
7	S ANURADHA	31	F	4 Y	PRES	EL	EL	NO	2 Y	4 Y	3/WEEK	PRES	EL	EL	N	NAD	Normal	1	NVBS	2.36	97	2.58	93	91	5.16	92	3.45	116
8	K M NAGAMMA	43	F	12 Y	PRES	PRES	NO	CO-2 D	8 Y	4 Y	3/WEEK	PRES	MC MT W	NO	N	NAD	Mild Restriction	2	CR+ WH+	1.53	66	1.78	65	100	2.92	88	1.86	68
9	RADHA N MURTY	56	F	6 Y	PRES	NO	NO	CO-1WK	6 Y	6 Y	3/WEEK	PRES	MCP	NO	N	NAD	Mild Restriction	1	NVBS	1.71	70	2.22	75	77	3.48	102	1.41	52
10	SHAMALA DEVI	23	F	10 Y	PRES	MC WR	NO	NO	10 Y	4Y	3/WEEK	PRES	MC WR	NO	N	NAD	Normal	1	NVBS	2.52	80	2.78	76	91	3.65	91	2.81	74
11	ABDUL GANI	45	M	6 Y	PRES	K WR	NO	ALL-1 Y	1 Y	3Y	NO	PRES	K WR	NO	N	NAD	Normal	1	NVBS	2.06	62	2.61	65	79	2.54	52	1.75	49
12	S.L.NARASIMHAN	37	M	4 Y	PRES	MC PP	NO	NO	4 Y	3 Y	3/WEEK	PRES	MC PP	NO	N	NAD	Mild Restriction	1	NVBS	3.47	102	3.92	96	89	8.22	99	4.63	125
13	SHAMEEN	33	F	5 Y	PRES	MC PP K	MC	NO	5 Y	5Y	2/WEEK	PRES	MC PP K	MC	N	NAD	Normal	1	NVBS	2.51	81	2.83	77	89	8.22	124	3.12	87
14	B S KAMALAMMA	53	F	12 Y	PRES	MC PP T	NO	NO	12 Y	3Y	NO	PRES	MC PP T	NO	N	NAD	Normal	1	CR+ WH+	1.44	70	1.65	67	87	3.91	76	1.79	75
15	SAVITRAMMA	50	F	14 Y	PRES	MC MT W	MC W	NO	2 Y	8 Y	3/WEEK	PRES	MC MT W	MC W	N	NAD	Mild Restriction	2	WH+	1.44	57	2.17	74	66	3.27	56	0.99	33
16	LAKSHMI S	62	F	15 Y	PRES	MC PP W	PP	NO	15 Y	4 Y	3/WEEK	PRES	MC PP W	PP	N	NAD	Mild Restriction	2	NVBS	0.88	38	1.26	45	70	2.3	69	0.51	20
17	SHAKUNTALA N	55	F	6 Y	PRES	PP W	NO	NO	6 Y	4 Y	4/WEEK	PRES	PP W	NO	N	NAD	Severe Restriction	1	NVBS	1.68	83	1.98	82	85	3.1	106	2	86
18	PREM	31	M	6Y	PRES	MC PP	NO	NO	6 MON	3 Y	3/WEEK	PRES	MC PP	NO	N	NAD	Normal	1	WH+	2.65	62	3.84	75	69	3.78	67	1.83	40
19	GANGANNA	65	M	12 Y	PRES	PP E WR	NO	VH-6 MON 6 I	8 Y	6 Y	3/WEEK	PRES	PP E WR	NO	N	Hyperinflation	Mild Obstruction	2	WH+	0.82	29	1.54	44	53	115	25	0.41	14
20	MURALI	51	M	5 Y	PRES	MC E MT	MC	NO	4 Y	4Y	3/WEEK	PRES	MC E MT	MC	N	NAD	Severe Obstruction	1	NVBS	1.83	71	2.73	87	67	5.8	80	1.05	37
21	KARTHIKEYAN	56	M	10 Y	PRES	MC K AN	MC	WH-1 Y	8 Y	9 Y	3/WEEK	PRES	MC K AN	MC	N	NAD	Mild Obstruction	2	WH+	1.43	47	2.83	75	51	5.36	68	0.7	72
22	SATHIYA	57	M	6 Y	PRES	NO	NO	NO	1 Y	3Y	3/WEEK	PRES	NO	NO	N	NAD	Moderate Restrictio	1	NVBS	1.48	65	2.27	81	65	4.27	69	0.87	34
23	SRIRAM	57	M	14 Y	PRES	MC PP W	PP W	NO	13 Y	5 Y	NO	PRES	MC PP W	PP W	N	Hyperinflation	Mild Obstruction	2	WH+	1.35	56	2.36	80	57	5.27	75	0.57	21
24	PRAVEEN	55	M	4 Y	PRES	NO	NO	NO	4 Y	4 Y	NO	PRES	NO	NO	N	NAD	Moderate Restrictio	1	NVBS	2.16	65	3.23	78	67	5.37	65	1.29	37
25	RATHINAM	54	M	5 Y	PRES	MC W E	MC	NO	4 Y	4 Y	3/WEEK	PRES	MC W E	MC	N	NAD	Mild Obstruction	1	NVBS	1.64	69	2.48	86	66	5.44	81	0.89	34

Ref.No.8102/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 09.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for September 2014 –
Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on September 12th 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following Project was approved by the Ethical Committee

Name of P.G.	Course	Name of the Project	Remarks
Dr.A.Arunkumar a.rubesh@gmail.com	PG in MD (General Medicine) Madurai Medical College & Govt. Rajaji Hospital, Madurai	**"A comparative study of Pulmonary function test abnormalities in treatment Naïve and patients on treatment with rheumatoid arthritis"**	**Approved**

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

Chairman
Ethical Committee

DEAN/Convenor 24-9-14
Madurai Medical College &
Govt. Rajaji Hospital, Madurai.

24-9-14

To
The above Applicant
-thro. Head of the Department concerned

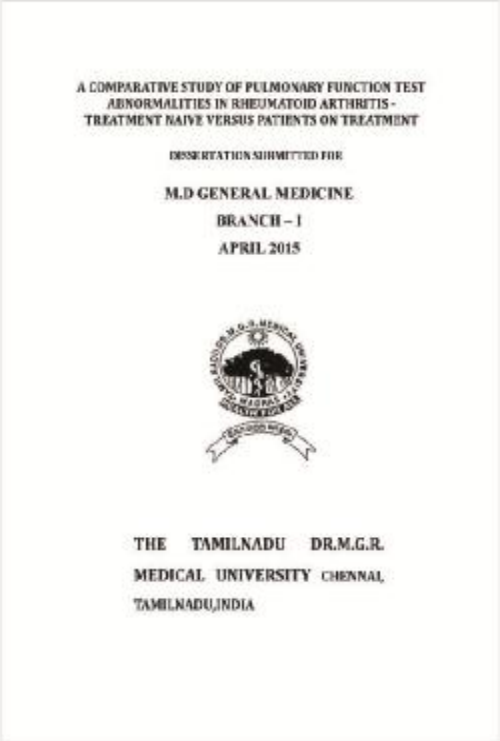
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	20111133 . M.d. General Medicine AR..
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	A COMPARATIVE STUDY OF PULM..
File name:	arun_final_thesis.docx
File size:	190.96K
Page count:	137
Word count:	13,370
Character count:	81,755
Submission date:	08-Oct-2014 11:34AM
Submission ID:	456561303



A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS - TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT

DISSERTATION SUBMITTED FOR

M.D GENERAL MEDICINE

BRANCH – I

APRIL 2015

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY CHENNAI, TAMILNADU,INDIA

A COMPARATIVE STUDY OF PULMONARY FUNCTION TEST ABNORMALITIES IN RHEUMATOID ARTHRITIS - TREATMENT NAIVE VERSUS PATIENTS ON TREATMENT

DISSERTATION SUBMITTED FOR

M.D GENERAL MEDICINE

BRANCH – I

APRIL 2015

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY CHENNAI, TAMILNADU,INDIA